10/130 Rw

FILE 'HOME' ENTERED AT 17:07:17 ON 04 JUN 2003

FILE 'REGISTRY' ENTERED AT 17:07:42 ON 04 JUN 2003
L1 3 S MIRTAZAPINE

FILE 'CAPLUS' ENTERED AT 17:08:32 ON 04 JUN 2003
E NON-STEROIDAL ANTIINFLAMMATORY/CT
E NSAID/CT
L2 0 S E3, E4
L3 48 S NON STEROID ANTIINFLAMMATORY
L4 6285 S NSAIDS OR NSAID OR (NON-STEROIDAL (S) (ANTI-INFLAMMATORY OR A
S 85650-52-8/RN OR 61364-37-2/RN OR 61337-87-9/RN OR MIRTAZAPIN

FILE 'REGISTRY' ENTERED AT 17:12:49 ON 04 JUN 2003
L5 1 S 61337-67-5/RN

FILE 'CAPLUS' ENTERED AT 17:12:49 ON 04 JUN 2003
L6 286 S L5

FILE 'REGISTRY' ENTERED AT 17:12:50 ON 04 JUN 2003
L7 1 S 82601-27-2/RN

FILE 'CAPLUS' ENTERED AT 17:12:50 ON 04 JUN 2003
L8 286 S L7
L9 352 S 85650-52-8/RN OR 61364-37-2/RN OR 61337-87-9/RN OR MIRTAZAPIN
L10 1 S L9 AND L4

FILE 'MEDLINE, JAPIO, BIOSIS, TOXCENTER, USPATFULL' ENTERED AT 17:13:42 ON 04 JUN 2003

FILE 'MEDLINE, EMBASE, JAPIO, BIOSIS, TOXCENTER, USPATFULL' ENTERED AT 17:13:55 ON 04 JUN 2003
L11 81870 S L4
L12 2842 S L9
L13 126 S L11 AND L12
L14 126 DUP REM L13 (0 DUPLICATES REMOVED)
E HEADACHE/CT
L15 62712 S E3,E4,E7
L16 616 S L11 AND L15
L17 115 S L15 AND L12
L18 0 S L16 AND L17
L19 544 DUP REM L16 (72 DUPLICATES REMOVED)
L20 110 DUP REM L17 (5 DUPLICATES REMOVED)
L21 45 S L19 AND TENSION
L22 3 S L20 AND TENSION
L23 126 FOCUS L14 1-

L21 ANSWER 7 OF 45 MEDLINE
ACCESSION NUMBER: 97060573 MEDLINE
DOCUMENT NUMBER: 97060573 PubMed ID: 8904620
TITLE: Self-medication of a single headache episode with ketoprofen, ibuprofen or placebo, home-monitored with an electronic patient diary.
AUTHOR: van Gerven J M; Schoemaker R C; Jacobs L D; Reints A; Ouwersloot-van der Meij M J; Hoedemaker H G; Cohen A F
CORPORATE SOURCE: Centre for Human Drug Research, Leiden University Hospital, The Netherlands.
SOURCE: BRITISH JOURNAL OF CLINICAL PHARMACOLOGY, (1996 Oct) 42 (4) 475-81.
Journal code: 7503323. ISSN: 0306-5251.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(RANDOMIZED CONTROLLED TRIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199702
ENTRY DATE: Entered STN: 19970305
Last Updated on STN: 19970305
Entered Medline: 19970218

AB 1. The objective of this study was to investigate the efficacy of home-medicated **non-steroidal anti-inflammatory** (**NSAID**) analgesics, using an electronic patient diary. Single doses of ketoprofen 25 mg and ketoprofen 50 mg were compared with ibuprofen 200 mg and placebo in the treatment of a single occasion of episodic **tension**-type headache, using a double-blind, randomized, parallel group design. 2. A total of 166 patients with headache compatible with episodic **tension**-type headache and no refractory headaches or contraindications to **NSAIDs** were contacted by advertisements and selected by questionnaires. Patients performed the study at home, using an electronic diary for headache assessment, with a form to allow comments and corrections. Visual analogue scales (VAS 10 cm) of headache severity, five-item headache relief rating (HRR) scales, and time of intake of 'escape' analgesics were scored regularly, for 4 h following intake of trial medication. 3. VAS-scores (n = 1407) and HRRs (n = 452) were returned by 159 patients. Of these scores, 1.5% were inadvertently omitted from the electronic diary or modified on the comment forms. 4. Headache (VAS and HRR) improved more with all three **NSAIDs** than with placebo, although the effect of ibuprofen was significant for HRR only. After 2 and 4 h respectively, the reduction in VAS-ratios was 17 and 19% with placebo, 18 and 53% with ibuprofen 200 mg, 41 and 61% with ketoprofen 25 mg, and 47 and 59% with ketoprofen 50 mg. After 4 h, headache improved strongly (highest HRR) in 18% of patients on placebo, 39% on ibuprofen 200 mg, 62% on ketoprofen 25 mg, and 55% on ketoprofen 50 mg. Headache disappeared completely (VAS-score = 0) in one patient (3%) with placebo (after 180 min), 10% with ibuprofen 200 mg (average 211 min), 18% with ketoprofen 25 mg (159 min), and 28% with ketoprofen 50 mg (146 min). 5. The effects of ketoprofen 50 mg were more pronounced than those of ibuprofen 200 mg, which seemed to start later. Ketoprofen 25 mg and 50 mg were very similar, suggesting a maximal effect of the lower dose. Mild to moderate adverse events were reported by 9% of the patients, half of which occurred with ketoprofen 50 mg. Treatment of headache with ketoprofen can start with 25 mg, and possibly less. 6. Although a direct comparative study would be necessary to determine the relative benefits of the novel electronic patient diaries over traditional paper-and-pencil methods, this study has shown the usefulness of this newer technique to detect differences in efficacy between low doses of analgesics under ambulant conditions, with very limited loss of data. Electronic patient

diaries appear to be an important new attribute for the efficacy assessment of self-medicated drugs.

L21 ANSWER 13 OF 45 MEDLINE
ACCESSION NUMBER: 85254878 MEDLINE
DOCUMENT NUMBER: 85254878 PubMed ID: 4016938
TITLE: Antimigraine drugs in the management of daily chronic headaches: clinical profiles of responsive patients.
AUTHOR: Micieli G; Piazza D; Sinforiani E; Cavallini A; Trucco M; Gabellini S; Mancuso A; Pacchetti C
SOURCE: CEPHALALGIA, (1985 May) 5 Suppl 2 219-24.
Journal code: 8200710. ISSN: 0333-1024.
PUB. COUNTRY: Norway
DOCUMENT TYPE: (CLINICAL TRIAL)
(CONTROLLED CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198509
ENTRY DATE: Entered STN: 19900320
Last Updated on STN: 19970203
Entered Medline: 19850916

AB Flunarizine, a Ca-antagonist with demonstrated antimigraine properties, and indoprofen, an **anti-inflammatory non-steroidal** agent, were used in the treatment of daily chronic headache. Forty-two migraineurs with interval headache (MIH) were treated with flunarizine in a 6-month open trial, while indoprofen was administered to 23 patients with MIH and 7 with chronic **tension** headache (CTH) in a 2-month, double-blind, cross-over placebo-controlled study. Flunarizine was found effective in over 65% of the patients, while indoprofen was able to improve headache severity in only 30% of the subjects. In the responder patients, the effectiveness of both drugs is more pronounced in MIH, and seems to be ascribable to the ability of the treatments to reduce number and severity of attacks. A higher incidence of previous affective disturbances is found in non-responsive cases. The analysis of factors converting episodic into chronic headache shows slight but not significant differences between responders and non-responders. An impairment of plasma beta-endorphin levels, in the presence of normal ACTH, cortisol and nociceptive RIII threshold values, characterizes daily chronic headache (DCH) patients. Moreover, indoprofen does not significantly affect these biological and neurophysiological parameters independently of the therapeutic response.

L21 ANSWER 14 OF 45 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 2002630313 MEDLINE
DOCUMENT NUMBER: 22275793 PubMed ID: 12387689
TITLE: Treatment of paediatric headache.
AUTHOR: Lewis Donald W; Scott David; Rendin Valerie
CORPORATE SOURCE: Department of Pediatrics, Division of Pediatric Neurology, Children's Hospital of the King's Daughters, Eastern Virginia Medical School, Norfolk, Virginia 23510, USA.. dLewis@chkd.com
SOURCE: Expert Opin Pharmacother, (2002 Oct) 3 (10) 1433-42. Ref: 37
Journal code: 100897346. ISSN: 1465-6566.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200303
ENTRY DATE: Entered STN: 20021022
Last Updated on STN: 20030304
Entered Medline: 20030303

AB Headaches are very common during childhood and become increasingly frequent during adolescence. The diagnosis of primary headache disorders (e.g., migraine and **tension**-type headache) rests principally on clinical criteria as set forth by the International Headache Society. Treatment options include acute or episodic measures, prophylactic agents and non-pharmacological or behavioural interventions. From review of available evidence, the most efficacious acute treatments of paediatric migraine include the **non-steroidal anti-inflammatory** agent ibuprofen at 7.5 - 10 mg/kg/dose or nasal sumatriptan at doses of 5 or 20 mg. For those patients with headaches that occur with sufficient frequency and severity to warrant daily prophylaxis, controlled data are limited. Agents which are likely to be beneficial include amitriptyline, flunarizine (not available in the US) and cyproheptadine. Clinical experience with the anti-epileptic agents topiramate and valproate suggests an expanding role for the prevention of paediatric migraine in the future.

L21 ANSWER 2 OF 45 MEDLINE
ACCESSION NUMBER: 2002167259 MEDLINE
DOCUMENT NUMBER: 21894766 PubMed ID: 11898510
TITLE: Treatment of childhood headaches.
AUTHOR: Gupta A; Rothner A D
CORPORATE SOURCE: Department of Child Neurology, Cleveland Clinic Foundation, 9500 Euclid Avenue, S-71, Cleveland, OH 44195, USA.. guptaa1@ccf.org
SOURCE: Curr Neurol Neurosci Rep, (2001 Mar) 1 (2) 144-54. Ref: 41
Journal code: 100931790. ISSN: 1528-4042.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200205
ENTRY DATE: Entered STN: 20020320
Last Updated on STN: 20020507
Entered Medline: 20020506

AB Migraine and **tension**-type headaches are two of the most common types of primary headache disorders in children. Migraine is a primary central nervous system disorder characterized by triggered or spontaneous

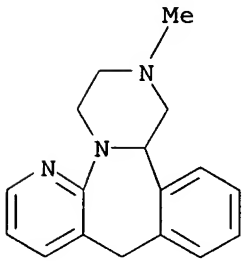
episodes of activation of trigemino-vascular complex, neurogenic inflammation around vessels and meninges, and stimulation of the peripheral and central pain pathways of the trigemino-cervical complex. The triptans, by their selective agonistic action on 5-HT1B/1D receptors, are very effective in the treatment of migraine pain and associated symptoms. Early studies on the safety and efficacy of triptans in the management of childhood migraine show encouraging results. We propose a stratified-care model for the management of migraine in children, and discuss pharmacotherapy based on the pathophysiologic mechanisms of migraine pain. Management of **tension**-type headaches requires comprehensive medical and psychologic evaluation and an individualized approach for a successful outcome.

L21 ANSWER 3 OF 45 MEDLINE
ACCESSION NUMBER: 2000215377 MEDLINE
DOCUMENT NUMBER: 20215377 PubMed ID: 10751917
TITLE: [Headache treatment in an emergency unit of the city of Ribeirao Preto, Brazil].
Tratamento da cefaleia em uma unidade de emergencia da cidade de Ribeirao Preto.
AUTHOR: Bigal M E; Bordini C A; Speciali J G
CORPORATE SOURCE: Faculdade de Medicina de Ribeirao Preto da Universidade de Sao Paulo (FMRP/USP).
SOURCE: ARQUIVOS DE NEURO-PSIQUIATRIA, (1999 Sep) 57 (3B) 813-9.
Journal code: 0125444. ISSN: 0004-282X.
PUB. COUNTRY: Brazil
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: Portuguese
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200004
ENTRY DATE: Entered STN: 20000427
Last Updated on STN: 20000427
Entered Medline: 20000420

AB Headache is one of the most common symptoms observed in clinical practice. It has a considerable economic impact and overburdens emergency rooms. In Brazil, most emergency rooms have no tryptans. The present study analyses the treatment provided by the Emergency Room of the University Hospital of Ribeirao Preto. In 1996, 1254 patients were treated for headache and 64 of them required hospitalization. Of the non-hospitalized (NH) patients, 77% had primary headache, as opposed to 29.7% of hospitalized patients. Of the patients with migraine, 83.6% improved with intravenous dipyrone, 66.7% improved with intramuscular diclofenac and 81.8% improved with intravenous chlorpromazine. The percentages of patients with **tension**-type headache who improved with the same drugs were 77.8%, 80% and 100%, respectively. Among NH patients, 16.3% improved without any medication. We conclude that the drugs used have similar efficacy profiles and costs and can be used at basic health unities. The major drawback is parenteral administration.

L21 ANSWER 4 OF 45 MEDLINE

L1 ANSWER 1 OF 3 REGISTRY COPYRIGHT 2003 ACS
RN 85650-52-8 REGISTRY
CN Pyrazino[2,1-a]pyrido[2,3-c][2]benzazepine, 1,2,3,4,10,14b-hexahydro-2-methyl- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Pyrazino[2,1-a]pyrido[2,3-c][2]benzazepine, 1,2,3,4,10,14b-hexahydro-2-methyl-, (.+-.)-
OTHER NAMES:
CN 6-Azamianserin
CN Mepirzapin
CN Mepirzepine
CN **Mirtazapine**
CN Mirtazepine
CN Mirtazipine
CN Org 3770
CN Promyrtil
CN Remergil
CN Remergon
CN Remeron
CN Rexer
CN Zispin
FS 3D CONCORD
DR 61337-67-5, 82601-27-2
MF C17 H19 N3
CI COM
SR Commission of European Communities
LC STN Files: ADISINSIGHT, ADISNEWS, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAPLUS, CASREACT, CBNB, CHEMCATS, CHEMLIST, CIN, CSCHEM, DDFU, DIOGENES, DRUGNL, DRUGPAT, DRUGU, DRUGUPDATES, EMBASE, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, MRCK*, MSDS-OHS, PHAR, PIRA, PROMT, RTECS*, SYNTHLINE, TOXCENTER, USAN, USPAT2, USPATFULL
(*File contains numerically searchable property data)
Other Sources: EINECS**, WHO
(**Enter CHEMLIST File for up-to-date regulatory information)



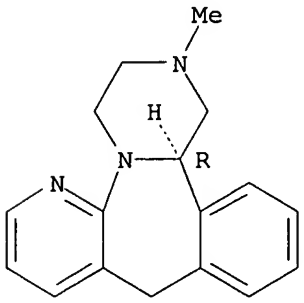
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

241 REFERENCES IN FILE CA (1957 TO DATE)
5 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
243 REFERENCES IN FILE CAPLUS (1957 TO DATE)

L1 ANSWER 2 OF 3 REGISTRY COPYRIGHT 2003 ACS
RN 61364-37-2 REGISTRY
CN Pyrazino[2,1-a]pyrido[2,3-c][2]benzazepine, 1,2,3,4,10,14b-hexahydro-2-methyl-, (14bR)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Pyrazino[2,1-a]pyrido[2,3-c][2]benzazepine, 1,2,3,4,10,14b-hexahydro-2-

methyl-, (R)-
OTHER NAMES:
CN **(-)-Mirtazapine**
CN (R)-6-Azamianserin
CN (R)-Org 3770
CN Org 44-19
FS STEREOSEARCH
MF C17 H19 N3
LC STN Files: BEILSTEIN*, CA, CAPLUS, CHEMLIST, DRUGPAT, DRUGUPDATES, IFICDB, IFIPAT, IFIUDB, TOXCENTER
(*File contains numerically searchable property data)
Other Sources: EINECS**
(**Enter CHEMLIST File for up-to-date regulatory information)

Absolute stereochemistry.

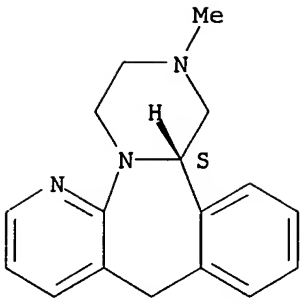


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

18 REFERENCES IN FILE CA (1957 TO DATE)
18 REFERENCES IN FILE CAPLUS (1957 TO DATE)

L1 ANSWER 3 OF 3 REGISTRY COPYRIGHT 2003 ACS
RN 61337-87-9 REGISTRY
CN Pyrazino[2,1-a]pyrido[2,3-c][2]benzazepine, 1,2,3,4,10,14b-hexahydro-2-methyl-, (14bS)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Pyrazino[2,1-a]pyrido[2,3-c][2]benzazepine, 1,2,3,4,10,14b-hexahydro-2-methyl-, (S)-
OTHER NAMES:
CN **(+)-Mirtazapine**
CN (S)-6-Azamianserin
CN (S)-Org 3770
CN Org 44-20
FS STEREOSEARCH
MF C17 H19 N3
LC STN Files: BEILSTEIN*, CA, CAPLUS, CHEMLIST, DRUGPAT, DRUGUPDATES, IFICDB, IFIPAT, IFIUDB, TOXCENTER
(*File contains numerically searchable property data)
Other Sources: EINECS**
(**Enter CHEMLIST File for up-to-date regulatory information)

Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

16 REFERENCES IN FILE CA (1957 TO DATE)
16 REFERENCES IN FILE CAPLUS (1957 TO DATE)

=>

3 ANSWER [redacted] OF 15 MEDLINE
ACCESSION NUMBER: 96318006 MEDLINE
DOCUMENT NUMBER: 96318006 PubMed ID: 8706118
TITLE: Low-dose **ibuprofen** in self-medication of mild to moderate headache: a comparison with acetylsalicylic acid and placebo.
AUTHOR: Nebe J; Heier M; Diener H C
CORPORATE SOURCE: Department of Neurology, University of Essen, Germany.
SOURCE: CEPHALALGIA, (1995 Dec) 15 (6) 531-5.
Journal code: 8200710. ISSN: 0333-1024.
PUB. COUNTRY: Norway
DOCUMENT TYPE: (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(RANDOMIZED CONTROLLED TRIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199609
ENTRY DATE: Entered STN: 19960919
Last Updated on STN: 19960919
Entered Medline: 19960912

AB A double-blind, threefold crossover, double-dummy trial was performed, investigating the efficacy of 200 mg **ibuprofen** compared with 500 mg acetylsalicylic acid and placebo in patients who usually treated their headaches with over-the-counter drugs. Ninety-five patients suffering from mild to moderate migraine or episodic **tension-type headache** were included. Seventy-seven patients entered the intention-to-treat analysis and 65 completed all three treatments. For the main response criterion, a minimum 50% decrease of headache intensity on a visual analogue scale at 1 h after treatment, **ibuprofen** was significantly superior to acetylsalicylic acid and placebo. This was true for migraine attacks and **tension-type headache** episodes. Towards the end of the observation period (150 min), the differences between **ibuprofen** and acetylsalicylic acid were no longer significant. In conclusion, **ibuprofen** was at least equivalent to acetylsalicylic acid and superior to placebo.

ACCESSION NUMBER: 2002399062 MEDLINE
DOCUMENT NUMBER: 22094940 PubMed ID: 12100095
TITLE: Acute and chronic hypertensive **headache** and hypertensive encephalopathy.
COMMENT: Comment in: Cephalalgia. 2003 Apr;23(3):238-9; author reply 239
AUTHOR: Spierings E L H
CORPORATE SOURCE: Department of Neurology, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA.. ESpierungs@partners.org
SOURCE: CEPHALALGIA, (2002 May) 22 (4) 313-6.
Journal code: 8200710. ISSN: 0333-1024.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200209
ENTRY DATE: Entered STN: 20020801
Last Updated on STN: 20030204
Entered Medline: 20020910
AB Three patients are described who experienced **headache** from hypertension: one had acute **headache** from acute hypertension, one had daily, morning **headaches** from chronic hypertension, and one had acute **headache** with generalized tonic-clonic seizure from hypertensive encephalopathy. The presumed pathophysiological mechanisms involved in the three hypertensive **headache** conditions are reviewed.

L3 ANSWER 1 OF 15 MEDLINE
ACCESSION NUMBER: 2003203458 MEDLINE
DOCUMENT NUMBER: 22608969 PubMed ID: 12723741
TITLE: Review of the analgesic efficacy of **ibuprofen**.
AUTHOR: Beaver William T
CORPORATE SOURCE: Georgetown University School of Medicine, Washington, DC, USA.
SOURCE: INTERNATIONAL JOURNAL OF CLINICAL PRACTICE. SUPPLEMENT, (2003 Apr) (135) 13-7. Ref: 18
Journal code: 9712380. ISSN: 1368-504X.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200306
ENTRY DATE: Entered STN: 20030502
Last Updated on STN: 20030605
Entered Medline: 20030604

AB There is a clear relationship between single doses of **ibuprofen** over the range 50-400 mg and the peak analgesic effect and the duration of analgesia. The smallest clinically useful dose of **ibuprofen** is 200 mg. **Ibuprofen** 400 mg has been shown to be as effective as aspirin 600 or 900 mg/day in models of moderate pain but superior to aspirin or paracetamol in more sensitive models such as dental pain. The duration of action of **ibuprofen** 400 mg is at least 6 hours compared with 4-6 hours for **ibuprofen** 200 mg or paracetamol. In patients undergoing oral surgery, **ibuprofen** 200 mg was broadly comparable with naproxen 220 mg and **ibuprofen** 400 mg comparable with ketoprofen 25 mg. The combination of **ibuprofen** and hydrocodone is more effective than either drug alone in patients undergoing abdominal and gynaecological surgery. The absorption of **ibuprofen** acid is influenced by formulation, and certain salts of **ibuprofen** (lysine, arginine, potassium) and solubilised formulations have an enhanced onset of activity. These differences are clinically important, offering a shorter time to onset of relief of **tension headache** compared with paracetamol.

L3 ANSWER 2 OF 15 MEDLINE
ACCESSION NUMBER: 2003089286 MEDLINE
DOCUMENT NUMBER: 22488880 PubMed ID: 12600797
TITLE: Low-dose diclofenac potassium in the treatment of episodic **tension-type headache**.
AUTHOR: Kubitzek Florian; Ziegler Gabrielle; Gold Morris S; Liu Jiun-Min H; Ionescu Elisabeta
CORPORATE SOURCE: Principal Investigator, Member of German Society of Pain Therapy (STK), Leopoldstr. 33, 80802, Munchen, Germany.
SOURCE: EUROPEAN JOURNAL OF PAIN, (2003) 7 (2) 155-62.
Journal code: 9801774. ISSN: 1090-3801.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(MULTICENTER STUDY)
(RANDOMIZED CONTROLLED TRIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200304
ENTRY DATE: Entered STN: 20030226
Last Updated on STN: 20030430
Entered Medline: 20030429

AB BACKGROUND: Several clinical trials have demonstrated that low doses of non-steroidal anti-inflammatory drugs relieve episodic **tension-type headache** (ETH). AIMS: The aims of this placebo-controlled study were to determine whether single doses of diclofenac-K 12.5 and 25mg effectively relieve ETH in adults and to compare it to **ibuprofen** 400mg. METHODS: A single-dose multicentre, randomised, double-blind, double-dummy, clinical trial was conducted at 22 primary care centres in Germany. All subjects had a history of ETH according to the classification of the International Headache Society. Of 684 subjects randomised, 620 used the study drugs for an episode of **tension headache** occurring within one month after enrolment: diclofenac-K 12.5mg (n=160), diclofenac-K 25mg (n=156), **ibuprofen** 400mg (n=151) and placebo (n=153). The primary efficacy variable was total pain relief, calculated as the time-weighted sum of the pain relief assessments from baseline to the 3h evaluation time (TOTPAR-3). RESULTS: For TOTPAR-3, all active treatments were superior to placebo; no statistically significant difference between the three active treatments could be detected. A similar pattern was also observed with regard to TOTPAR-6 (6h evaluation time), > or =50%maxTOTPAR at 3 and 6h, weighted pain intensity difference at 3 and 6h (SPID-3; SPID-6), percentage of patients with complete headache relief at 2h, end of study global evaluation and time to rescue medication. The number-needed-to-treat (NNT) at 6h was 4.5 (2.9-9.2) in the **ibuprofen** 400mg group, 4.0 (2.8-7.3) in the diclofenac-K 12.5mg group and 3.9 (2.7-7.1) in the diclofenac-K 25mg group. These differences were not statistically significant.CONCLUSION: Diclofenac-K, administered as single doses of 12.5 and 25mg effectively relieves ETH and is comparable to **ibuprofen** 400mg.

L3 ANSWER 3 OF 15 MEDLINE

ACCESSION NUMBER: 2002630313 MEDLINE
DOCUMENT NUMBER: 22275793 PubMed ID: 12387689
TITLE: Treatment of paediatric headache.
AUTHOR: Lewis Donald W; Scott David; Rendin Valerie
CORPORATE SOURCE: Department of Pediatrics, Division of Pediatric Neurology, Children's Hospital of the King's Daughters, Eastern Virginia Medical School, Norfolk, Virginia 23510, USA.. dLewis@chkd.com
SOURCE: Expert Opin Pharmacother, (2002 Oct) 3 (10) 1433-42. Ref: 37
Journal code: 100897346. ISSN: 1465-6566.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200303
ENTRY DATE: Entered STN: 20021022
Last Updated on STN: 20030304
Entered Medline: 20030303

AB Headaches are very common during childhood and become increasingly frequent during adolescence. The diagnosis of primary headache disorders (e.g., migraine and **tension-type headache**) rests principally on clinical criteria as set forth by the International Headache Society. Treatment options include acute or episodic measures, prophylactic agents and non-pharmacological or behavioural interventions. From review of available evidence, the most efficacious acute treatments of paediatric migraine include the non-steroidal anti-inflammatory agent **ibuprofen** at 7.5 - 10 mg/kg/dose or nasal sumatriptan at doses of 5 or 20 mg. For those patients with headaches that occur with sufficient frequency and severity to warrant daily prophylaxis, controlled data are

limited. Agents which are likely to be beneficial include amitriptyline, flunarizine (not available in the US) and cyproheptadine. Clinical experience with the anti-epileptic agents topiramate and valproate suggests an expanding role for the prevention of paediatric migraine in the future.

L3 ANSWER 4 OF 15 MEDLINE
ACCESSION NUMBER: 2002112899 MEDLINE
DOCUMENT NUMBER: 21834251 PubMed ID: 11845341
TITLE: [Treatment of idiopathic headache in childhood - recommendations of the German Migraine and Headache Society (DMKG)].
Therapie idiopathischer Kopfschmerzen im Kindesalter. Empfehlungen der Deutschen Migrane-und Kopfschmerzgesellschaft (DMKG).
AUTHOR: Evers S; Pothmann R; Uberall M; Naumann E; Gerber W D
CORPORATE SOURCE: Klinik und Poliklinik fur Neurologie, Westfalische Wilhelms-Universitat Munster, Germany.. everss@uni-muenster.de
SOURCE: Schmerz, (2002 Feb) 16 (1) 48-56. Ref: 95
Journal code: 8906258. ISSN: 0932-433X.
PUB. COUNTRY: Germany: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: German
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200204
ENTRY DATE: Entered STN: 20020215
Last Updated on STN: 20020413
Entered Medline: 20020412

AB According to the principles of evidence-based medicine, the controlled studies on the treatment of idiopathic headache in childhood have been analysed and compiled to treatment recommendations. For the acute treatment of migraine attacks or **tension-type headache, ibuprofen** (10 mg per kg body weight) or acetaminophen (15 mg per kg body weight) are recommended with highest evidence, intranasal sumatriptan (10 to 20 mg) can be given as second choice. For the prophylaxis of migraine, betablockers (propranolol and metoprolol), flunarizine, and valproic acid are recommended. Flunarizine is the drug of first choice in the treatment of migraine-related disorders. No controlled studies are available for the treatment of further headache types. First line methods for the non-drug treatment of headache in childhood are relaxation therapies, biofeedback, and specific training schedules.

L3 ANSWER 5 OF 15 MEDLINE
ACCESSION NUMBER: 2001512968 MEDLINE
DOCUMENT NUMBER: 21444791 PubMed ID: 11560814
TITLE: The use of **ibuprofen** plus caffeine to treat **tension-type headache**.
AUTHOR: Diamond S; Freitag F G
CORPORATE SOURCE: Diamond Headache Clinic, 467 West Deming Place, Suite 500, Chicago, IL 60614-1726, USA.. MACF48@aol.com
SOURCE: Curr Pain Headache Rep, (2001 Oct) 5 (5) 472-8.
Journal code: 100970666. ISSN: 1531-3433.
PUB. COUNTRY: United States
DOCUMENT TYPE: (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(MULTICENTER STUDY)
(RANDOMIZED CONTROLLED TRIAL)
LANGUAGE: English

FILE SEGMENT: Priority Journals
ENTRY MONTH: 200112
ENTRY DATE: Entered STN: 20010919
Last Updated on STN: 20020122
Entered Medline: 20011204

AB Simple analgesics such as **ibuprofen**, aspirin, and acetaminophen have long been used in the treatment of **tension-type headache**. Studies of combination agents of aspirin with caffeine or acetaminophen with caffeine have also demonstrated efficacy as analgesic agents. Other evidence also suggests that caffeine may have an analgesic effect unto itself in the relief of pain. We undertook the direction of a multicenter, double-blind, placebo-controlled, parallel trial to assess the efficacy and safety of **ibuprofen** combined with caffeine in the treatment of **tension-type headache**. The study was designed to also verify the analgesic efficacy of caffeine and further assess the role of **tension-type headache** as a model for the study of pain.

L3 ANSWER 6 OF 15 MEDLINE
ACCESSION NUMBER: 2001154426 MEDLINE
DOCUMENT NUMBER: 21071829 PubMed ID: 11200807
TITLE: Clinical management of young patients presenting with headache.
AUTHOR: Wober C; Wober-Bingol C
CORPORATE SOURCE: Department of Neuropsychiatry of Childhood and Adolescence, University of Vienna, Austria.
SOURCE: FUNCTIONAL NEUROLOGY, (2000) 15 Suppl 3 89-105. Ref: 79
Journal code: 8707746. ISSN: 0393-5264.
PUB. COUNTRY: Italy
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200103
ENTRY DATE: Entered STN: 20010404
Last Updated on STN: 20010404
Entered Medline: 20010322

AB Headache is a common symptom in young patients and requires a clearly structured, individual approach. The history and the clinical examination are prerequisites for planning further management of the condition. The IHS classification is particularly useful in the differential diagnosis of idiopathic headache. Additional diagnostic testing should not be performed routinely, but on an individual basis depending on the patient's history and neurological findings. The acute therapy of idiopathic headache in young patients has been evaluated in few studies only. However, there is general agreement that (in subjects requiring medication) paracetamol, acetylsalicylic acid and **ibuprofen** are most useful for treating migraine attacks, whereas analgesics should widely be avoided in **tension-type headache**.
For the prophylaxis of migraine and **tension-type headache**, non-pharmacological measures such as regulation of lifestyle, relaxation training and psychological or psychotherapeutic interventions are much more important than pharmacotherapy, which is required in a small number of patients only.

L3 ANSWER 7 OF 15 MEDLINE
ACCESSION NUMBER: 2001112752 MEDLINE
DOCUMENT NUMBER: 20580592 PubMed ID: 11139755
TITLE: [Treatment of **tension headache**].
Traitement des cephalees de tension.
AUTHOR: Schoenen J

CORPORATE SOURCE: Universite de Liege, Belgique.. schoenen.j@village.unnet.be
SOURCE: REVUE NEUROLOGIQUE, (2000) 156 Suppl 4 4S87-92. Ref: 31
Journal code: 2984779R. ISSN: 0035-3787.
PUB. COUNTRY: France
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: French
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200102
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20010208

AB The scientific basis of **tension- type headache** suffers from the lack of precise pathophysiological knowledge and the heterogenecity of this disorder. Treatment of acute **tension-type headache** episodes is more effective with an NSAIDs (**ibuprofen** 400-800mg, naproxen 550-825mg, ketoprofen 50-75mg) than with aspirin or paracetamol. Caffein containing preparations of NSAIDs are slightly superior, but should not be taken frequently to avoid headache chronification. For chronic **tension-type headache**, relaxation therapies with EMG biofeedback and tricyclics have about the same efficacy rate of 40-50p.100. Physical therapy and acupuncture are in general less effective. There is thus clearly a need for better strategies, e.g. combination of available therapies and novel approaches.

L3 ANSWER 8 OF 15 MEDLINE
ACCESSION NUMBER: 2001107328 MEDLINE
DOCUMENT NUMBER: 21036797 PubMed ID: 11195471
TITLE: Is the combination of **ibuprofen** and caffeine effective for the treatment of a **tension-type headache**?.
AUTHOR: Sparano N
CORPORATE SOURCE: Wyoming Valley Family Practice Residency, Kingston, Pennsylvania, USA.. sparano@wilkes.edu
SOURCE: JOURNAL OF FAMILY PRACTICE, (2001 Jan) 50 (1) 10.
Journal code: 7502590. ISSN: 0094-3509.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200102
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20010208

L3 ANSWER 9 OF 15 MEDLINE
ACCESSION NUMBER: 2001056231 MEDLINE
DOCUMENT NUMBER: 20398118 PubMed ID: 10940094
TITLE: Solubilized **ibuprofen**: evaluation of onset, relief, and safety of a novel formulation in the treatment of episodic **tension-type headache**.
AUTHOR: Packman B; Packman E; Doyle G; Cooper S; Ashraf E; Koronkiewicz K; Jayawardena S
CORPORATE SOURCE: Institute for Applied Pharmaceutical Research, Philadelphia, PA, USA.
SOURCE: HEADACHE, (2000 Jul-Aug) 40 (7) 561-7.
Journal code: 2985091R. ISSN: 0017-8748.
PUB. COUNTRY: United States
DOCUMENT TYPE: (CLINICAL TRIAL)

Journal; Article; (JOURNAL ARTICLE)
(RANDOMIZED CONTROLLED TRIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200012
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20001221

AB OBJECTIVE: To evaluate the relative efficacy of a new solubilized formulation of **ibuprofen** compared with acetaminophen caplets. METHODS: This double-blind, randomized, parallel group study evaluated 154 subjects taking a single dose of solubilized **ibuprofen**, 400 mg; acetaminophen, 1000 mg; or placebo for the relief of episodic **tension-type headache**. Time to relief was measured using a stopwatch, and overall efficacy was measured using traditional categorical pain and relief scales. RESULTS: **Ibuprofen** capsules (liquigel), 400 mg, were significantly faster than both acetaminophen, 1000 mg, and placebo for all time-to-relief measures. **Ibuprofen** liquigel had a median time to first perceptible pain relief of 39 minutes compared with 47 minutes for acetaminophen and 113 minutes for placebo. For median time to meaningful relief, **ibuprofen** liquigel had a time of 39 minutes compared with 53 minutes for acetaminophen and more than 180 minutes for placebo (P</=.02 for both measures). In addition, **ibuprofen** liquigels demonstrated significantly superior overall analgesic efficacy compared with acetaminophen, 1000 mg, for the relief of episodic **tension-type headache**. Both active treatments had a side effect profile similar to placebo. CONCLUSIONS: Although several other studies have demonstrated the overall analgesic superiority of **ibuprofen** to acetaminophen, this study demonstrated that the liquigel formulation also provides a clinically relevant advantage for time to analgesic effects.

L3 ANSWER 10 OF 15 MEDLINE
ACCESSION NUMBER: 2000462362 MEDLINE
DOCUMENT NUMBER: 20466341 PubMed ID: 11014413
TITLE: **Ibuprofen** plus caffeine in the treatment of **tension-type headache**.
AUTHOR: Diamond S; Balm T K; Freitag F G
CORPORATE SOURCE: Diamond Headache Clinic, Chicago, IL 60614-1726, USA.
SOURCE: CLINICAL PHARMACOLOGY AND THERAPEUTICS, (2000 Sep) 68 (3) 312-9.
Journal code: 0372741. ISSN: 0009-9236.
PUB. COUNTRY: United States
DOCUMENT TYPE: (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(MULTICENTER STUDY)
(RANDOMIZED CONTROLLED TRIAL)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200010
ENTRY DATE: Entered STN: 20001027
Last Updated on STN: 20001027
Entered Medline: 20001017

AB BACKGROUND: The effectiveness of caffeine as an adjuvant to **ibuprofen** has been documented in investigations of acute pain. Our objectives were to assess this agent in the treatment of **tension-type headache** and to establish clinical trial methods capable of assessing this agent in comparison with various **tension headache** treatments. Stopwatch technology was used for measurement techniques. METHODS: A randomized, double-blind, parallel, multicenter, single-dose, placebo- and

active-controlled study included 301 subjects diagnosed with **tension-type headache**. Treatment groups included **ibuprofen** and caffeine, **ibuprofen** alone, caffeine alone, or placebo. Subjects measured onset of relief (both time to first perceptible relief and time to meaningful relief) after taking a single oral dose of their assigned medication. Pain intensity and pain relief were rated over a 6-hour study period. Overall evaluation was made on completion of all other ratings. RESULTS: **Ibuprofen** and caffeine administered together provided significantly greater analgesic activity than **ibuprofen** alone, caffeine alone, and placebo. **Ibuprofen** and caffeine administered together demonstrated significantly shorter times to meaningful improvement in headache relief than **ibuprofen** or placebo; significantly greater total analgesia than **ibuprofen** alone, caffeine alone, or placebo; and significantly greater peak relief than **ibuprofen** alone, caffeine alone, or placebo. Significantly more subjects obtained meaningful headache relief with **ibuprofen** and caffeine administered together than with **ibuprofen** alone or placebo. More patients reported complete headache relief with **ibuprofen** and caffeine administered together than with **ibuprofen** alone, caffeine alone, or placebo. **Ibuprofen** and caffeine administered together was rated significantly better by patients than either **ibuprofen** alone, caffeine alone, or placebo. No subjects ended participation in the study early because of adverse events. CONCLUSIONS: Sensitive methods have been introduced to assess differences in analgesia among over-the-counter analgesic agents in relieving **tension-type headache** pain. A double-blind study with this method suggests that **ibuprofen** and caffeine administered together provides greater analgesic effectiveness than either component alone.

L3 ANSWER 11 OF 15 MEDLINE
ACCESSION NUMBER: 97165607 MEDLINE
DOCUMENT NUMBER: 97165607 PubMed ID: 9013368
TITLE: Nonprescription **ibuprofen** and acetaminophen in the treatment of **tension-type headache**.
AUTHOR: Schachtel B P; Furey S A; Thoden W R
CORPORATE SOURCE: Department of Epidemiology and Biostatistics, McGill University, Montreal, Canada.
SOURCE: JOURNAL OF CLINICAL PHARMACOLOGY, (1996 Dec) 36 (12) 1120-5.
Journal code: 0366372. ISSN: 0091-2700.
PUB. COUNTRY: United States
DOCUMENT TYPE: (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(RANDOMIZED CONTROLLED TRIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199704
ENTRY DATE: Entered STN: 19970424
Last Updated on STN: 19970424
Entered Medline: 19970417

AB A single-dose, double-blind, randomized clinical trial was conducted to examine the relative analgesic effectiveness of 400 mg of **ibuprofen** (n = 153), 1,000 mg of acetaminophen (n = 151), and placebo (n = 151) in volunteers with muscle contraction headache. At regular intervals during a 4-hour period, participants evaluated headache pain intensity on a 100-mm visual analog scale and headache pain relief on a six-category scale. Both active agents were significantly different from placebo at all time points and in reducing pain intensity and providing relief of headache overall. Similarly, **ibuprofen** at

400 mg differed significantly from acetaminophen at 1,000 mg on both rating scales. Participants receiving **ibuprofen** at 400 mg achieved complete relief of headache faster than those receiving acetaminophen at 1,000 mg or placebo, and more participants taking **ibuprofen** experienced complete relief of headache than those taking placebo or acetaminophen. Both **ibuprofen** at 400 mg and acetaminophen at 1,000 mg are efficacious analgesic agents for muscle contraction headache, and **ibuprofen** at 400 mg is significantly more effective than acetaminophen at 1,000 mg for treating this condition.

L3 ANSWER 12 OF 15 MEDLINE
ACCESSION NUMBER: 97060573 MEDLINE
DOCUMENT NUMBER: 97060573 PubMed ID: 8904620
TITLE: Self-medication of a single headache episode with ketoprofen, **ibuprofen** or placebo, home-monitored with an electronic patient diary.
AUTHOR: van Gerven J M; Schoemaker R C; Jacobs L D; Reints A; Ouwersloot-van der Meij M J; Hoedemaker H G; Cohen A F
CORPORATE SOURCE: Centre for Human Drug Research, Leiden University Hospital, The Netherlands.
SOURCE: BRITISH JOURNAL OF CLINICAL PHARMACOLOGY, (1996 Oct) 42 (4) 475-81.
Journal code: 7503323. ISSN: 0306-5251.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(RANDOMIZED CONTROLLED TRIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199702
ENTRY DATE: Entered STN: 19970305
Last Updated on STN: 19970305
Entered Medline: 19970218

AB 1. The objective of this study was to investigate the efficacy of home-medicated non-steroidal anti-inflammatory (NSAID) analgesics, using an electronic patient diary. Single doses of ketoprofen 25 mg and ketoprofen 50 mg were compared with **ibuprofen** 200 mg and placebo in the treatment of a single occasion of episodic **tension-type headache**, using a double-blind, randomized, parallel group design. 2. A total of 166 patients with headache compatible with episodic **tension-type headache** and no refractory headaches or contraindications to NSAIDs were contacted by advertisements and selected by questionnaires. Patients performed the study at home, using an electronic diary for headache assessment, with a form to allow comments and corrections. Visual analogue scales (VAS 10 cm) of headache severity, five-item headache relief rating (HRR) scales, and time of intake of 'escape' analgesics were scored regularly, for 4 h following intake of trial medication. 3. VAS-scores (n = 1407) and HRRs (n = 452) were returned by 159 patients. Of these scores, 1.5% were inadvertently omitted from the electronic diary or modified on the comment forms. 4. Headache (VAS and HRR) improved more with all three NSAIDs than with placebo, although the effect of **ibuprofen** was significant for HRR only. After 2 and 4 h respectively, the reduction in VAS-ratios was 17 and 19% with placebo, 18 and 53% with **ibuprofen** 200 mg, 41 and 61% with ketoprofen 25 mg, and 47 and 59% with ketoprofen 50 mg. After 4 h, headache improved strongly (highest HRR) in 18% of patients on placebo, 39% on **ibuprofen** 200 mg, 62% on ketoprofen 25 mg, and 55% on ketoprofen 50 mg. Headache disappeared completely (VAS-score = 0) in one patient (3%) with placebo (after 180 min), 10% with **ibuprofen** 200 mg (average 211 min), 18% with ketoprofen 25 mg (159 min), and 28% with ketoprofen 50 mg (146 min). 5. The effects of ketoprofen 50 mg were more pronounced than those of **ibuprofen**

200 mg, which seemed to start later. Ketoprofen 25 mg and 50 mg were very similar, suggesting a maximal effect of the lower dose. Mild to moderate adverse events were reported by 9% of the patients, half of which occurred with ketoprofen 50 mg. Treatment of headache with ketoprofen can start with 25 mg, and possibly less. 6. Although a direct comparative study would be necessary to determine the relative benefits of the novel electronic patient diaries over traditional paper-and-pencil methods, this study has shown the usefulness of this newer technique to detect differences in efficacy between low doses of analgesics under ambulant conditions, with very limited loss of data. Electronic patient diaries appear to be an important new attribute for the efficacy assessment of self-medicated drugs.

This is **G o o g l e**'s cache of http://www.angelfire.com/journal2/sadhelp/mirtazapine.htm.
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These search terms have been highlighted: mirtazapine headache

I know a lot of people here are on antidepressants for anxiety/depression/FB/FF/HH but get sexual dysfunction or find it ineffective. There is a newer antidepressant called **Mirtazapine which works on the same primary receptor (alpha2-adrenergic autoreceptor) as clonidine** however paradoxically as an antagonist (the theory that there is an alpha2 **dysregulation** not simply an excess or deficiency). It recently has been shown to help hot flushes like clonidine was many years ago. It also increases serotonin similar to SSRIs, Prozac, Paxil etc with significantly less risk of sexual dysfunction but can cause some more rapid weight gain in some (thought through an increase in appetite more than metabolism) & sedation so best taken around bedtime. **Clonidine** (the alpha2-agonist) also can exacerbate depression in some as mentioned in the CME article & links at this site and **should not be used at the same time as mirtazapine**. Some who have trouble finding a doctor to prescribe clonidine may find it easier to get a prescription for this antidepressant. It also is supposed to have a faster onset of action than SSRIs/older ADs and side effects often improve with the higher doses. Below is a recent abstract & if anyone decides to try it with their MD's guidance, report back. For pain here.

Treatment of **hot flushes** with **mirtazapine**: four case reports [In Process Citation]

*** New Article - Maturitas 2000 Oct 31;36(3):165-8** (ISSN: 0378-5122)

Waldinger MD; Berendsen HH; Schweitzer DH
Department of Psychiatry and Neurosexology, Leyenburg Hospital, Leyweg 275, 2545 CH, The Hague, The Netherlands.

Objective: To evaluate the effect of **mirtazapine** on the severity of **hot flushes** and bouts of **perspiration** in women. Method: In two women **with depression** a reduction in **hot flushes** was noticed by serendipity during treatment with **mirtazapine** 15-30 mg/daily. On the basis of this observation clinical studies were extended with two **non-depressed and non-anxious women with hot flushes**. Both subjects were prescribed **mirtazapine** daily. Results: Four cases are described as case reports. **All subjects reported a practically complete disappearance of hot flushes and associated perspiration, within the first week of treatment. Conclusion: Mirtazapine appears to have a substantial ameliorating effect on hot flushes and perspiration bouts.** It is postulated that the 5-HT(2A) blocking properties of **mirtazapine** is accounted in the symptomatic relief of **hot flushes**. In addition it is hypothesized that the serotonergic system is crucially involved in the pathogenesis of **hot flushes and perspiration bouts**. Further evaluation in double-blind placebo-controlled studies is encouraged.

Language: English
MEDLINE Indexing Date: 200011
Publication Type: MEDLINE RECORD IN PROCESS
Publication Type: JOURNAL ARTICLE

PreMedline Identifier: 0011063897
Unique NLM Identifier: 20519842

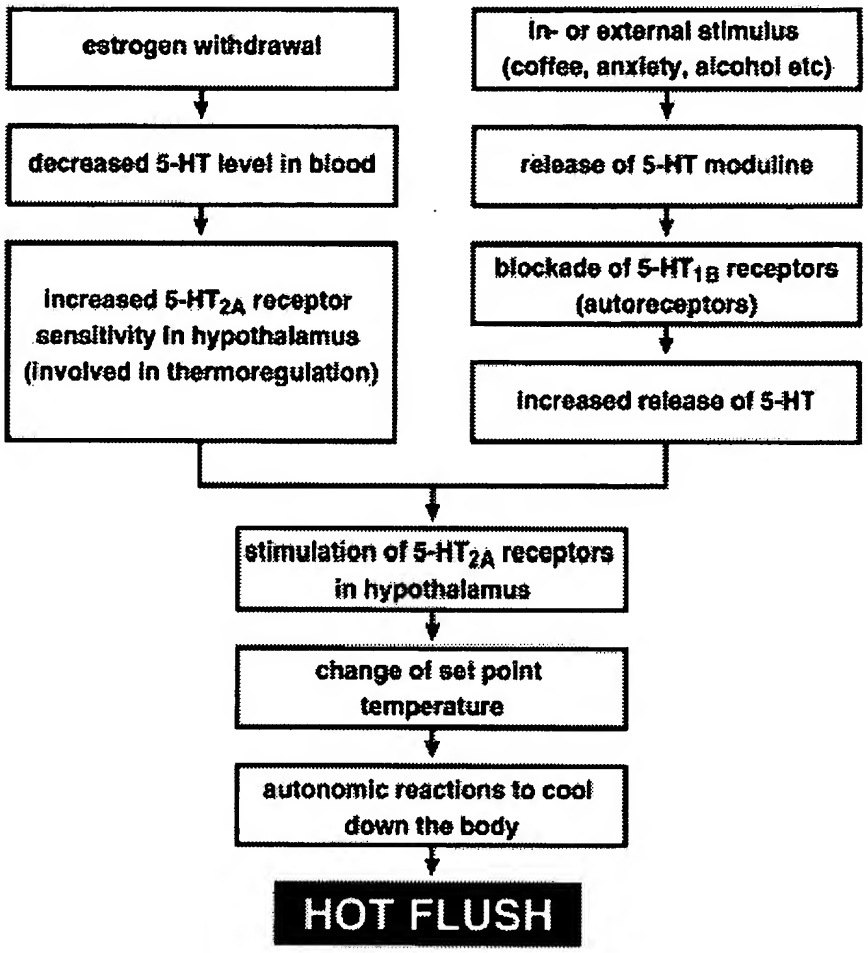

Fig. 1. Possible mechanism by which a hot flush is induced.

Here's an interesting article that tries to explain the interaction of hormones & neurotransmitters. Much of what is known about flushing is from studying menopausal hot flushes. From clonidine to antidepressants:

http://www.science.com.br/henrys_corner/artigos_tecnicos/the_role_of_serotonin_in_hot_flushes.pdf *

If down: http://www.angelfire.com/journal2/sadhelp/shf.pdf
(* Requires Adobe Acrobat since in .pdf format - Free Acrobat readers at http://www.acrobat.com)

My initial impression of the article is that while I can appreciate the scope of it, I feel their 5HT2A hypothesis is oversimplistic. If it were that simple then nefazodone/Serzone would likely have popped up as promptly effective for hot flushes already. It is considered a decent antidepressant at the right dose but not very effective for panic or anxiety but does not generally cause sexual dysfunction or weight gain so it may be worth a trial. Serzone unfortunately interacts with a lot of meds like Xanax so that should be looked at prior.

Remeron/mirtazapine has had some positive reports in the literature & mixed reviews anecdotally from rosacea flushers, some respond well while others don't at all. This may be because it blocks 5HT2, & 5HT3-like ondansetron/Zofran (reported effective anecdotally for erythematous rosacea & ocular rosacea) as well as histamine; what could be negating benefit is that it is primarily an

Alpha2NE-Antagonist (opposite of clonidine -used for hot flushes & anxiety). Interactions have been noted for **mirtazapine** & clonidine. If it works well it could also be normalizing a dysfunctional alpha2 autoreceptor. Also some selective alpha2NE-antagonists have been shown to be anxiolytic (anti-anxiety) while less specific antagonists are not:

Life Sci 1994;54(10):PL179-PL184 Related Articles, Books

The alpha-2 antagonists idazoxan and rauwolscine but not yohimbine or piperoxan are anxiolytic in the Vogel lick-shock conflict paradigm following intravenous administration.

La Marca S, Dunn RW.

Anaquest, Inc., Murray Hill, NJ 07974.

The **alpha 2 agonist clonidine has been shown to be anxiolytic in a number of preclinical anxiety models**. Interestingly, intravenous infusion of the alpha 2 antagonists idazoxan at 10 mg/kg and rauwolscine at 2.24 mg/kg significantly disinhibited lick-shock conflict responding in rats similar to the alpha 2 agonist clonidine (0.022 mg/kg) and the benzodiazepine diazepam (0.5 mg/kg). However, the alpha 2 antagonists yohimbine and piperoxan, the alpha 2 agonists medetomidine, guanfacine, and guanabenz, the non-specific alpha antagonist phentolamine, and the alpha 1 antagonist prazosin did not disinhibit conflict responding in the Vogel lick-shock paradigm. *In fact, yohimbine has been shown to be anxiogenic in both animals and man. This may be due to yohimbine's lack of specificity and its ability to inhibit GABAergic release*. In addition, all of these agents, except idazoxan, did not increase water consumption in water deprived rats. Idazoxan (10 mg/kg) significantly decreased water consumption by 45%. Therefore, idazoxan increased conflict responding for water reward at a dose (10 mg/kg) which also decreased water consumption in a non-conflict paradigm. **These data suggest that agents with selective antagonism at the alpha 2 receptor site may be anxiolytic while agents with less specificity at this site such as yohimbine, piperoxan, and phentolamine are not anxiolytic.**

PMID: 7906377 [PubMed - indexed for MEDLINE]

Since **mirtazapine** blocks clonidine it is likely not very selective however (yet still has reported anxiolytic effects):

Abo-Zena RA, Bobek MB, Dweik RA. Related Articles

Hypertensive urgency induced by an interaction of **mirtazapine** and clonidine.
Pharmacotherapy. 2000 Apr;20(4):476-8.
PMID: 10772378 [PubMed - indexed for MEDLINE]

Bengtsson HJ, Kele J, Johansson J, Hjorth S. Related Articles

Interaction of the antidepressant **mirtazapine** with alpha2-adrenoceptors modulating the release of 5-HT in different rat brain regions in vivo.
Naunyn Schmiedebergs Arch Pharmacol. 2000 Nov;362(4-5):406-12.
PMID: 11111835 [PubMed - indexed for MEDLINE]

We are still learning about neurotransmitters, their subtypes, interaction with other neurotransmitter

systems & how psychotropics work. Remeron is considered effective for serious depression & again mixed reviews for anxiety with low incidence of sexual dysfunction commonly associated with SSRIs but more commonly causes increased hunger/weight gain.

What is Remeron®?

(or REMERGIL, REXER, PROMYRTIL AS IT IS CALLED IN OTHER COUNTRIES, PLEASE FIND A LIST AT THE END OF THIS SECTION)

Remeron® is the tradename of Organon's new antidepressant **mirtazapine**.

Remeron® is the first NaSSA - a Noradrenergic and Specific Serotonergic Antidepressant. It enhances the release of the neurotransmitter noradrenaline in certain areas in the brain. It also increases the release of another neurotransmitter, serotonin. Such dual action is increasingly being recognised as beneficial for effectiveness in treating depression.

Remeron® is not associated with anticholinergic side effects like constipation, urinary retention and dizziness. In addition, Remeron's action on the serotonergic system is highly specific: it allows the extra serotonin to act on the serotonin receptor site which mediates the antidepressant activity, and it blocks other serotonin receptors which cause the unwanted serotonergic side effects like sexual dysfunction, insomnia, anxiety, agitation, and gastrointestinal disorders like nausea.

The most common side effects of Remeron® are daytime sleepiness which usually subsides rapidly after the first week and in some cases increased appetite and weight gain in some cases.

It is advised to take your daily dose of Remeron at night before going to bed. Of course, you should discuss use of Remeron® and any other questions you may have about Remeron or depression with your doctor.

Where is Remeron® available ?

Remeron is available in following countries.

Country Trade name
Argentina Remeron®
Austria Remeron®
Brazil Remeron®
Chile Promyrtil®
Ecuador Remeron®
Denmark Remeron®
Finland Remeron®
France Norset®
Germany Remergil®
Greece Remeron®
Hong Kong Remeron®
Italy Remeron®
Netherlands Remeron®
Peru Remeron®
Portugal Remeron®
Rep. Ireland Zispin®

Singapore Remeron®
Spain Rexer®
Sweden Remeron®
Turkey Remeron®
United Kingdom Zispin®
USA Remeron®

More info for consumers & medical professionals at:

http://www.remeron.com

>are you saying that **Mirtazapine** might help FF ?

--->That's what the medline report suggests FF/HH & one may infer FB.

>what do you mean with "It recently has been shown to help hot flushes like CLONIDINE WAS MANY YEARS AGO" ? doesnt it still help flushing ? why did it stop ?

--->Clonidine was shown to help in a study/report like this except this medication (**Mirtazapine** is the chemical name) also is an antidepressant with anti-anxiety effects. For this reason some docs may be more comfortable prescribing it. The sentence doesn't imply clonidine has suddenly become ineffective:) but clonidine can aggravate depression in some. Of interest they both work on the alpha2-adrenergic autoreceptor. **Mirtazapine** also increases serotonin however similar to SSRIs without sexual dysfunction & insomnia (sleep is generally improved on this).

>"can cause some weight gain in some (thought through an increase in appetite" thats good... i really need more weight.

--->Some find their appetite increased on **mirtazapine** & may gain some weight.

>going to my doc the 19/03, and im wondering what to ask for. i got this list with medicines that might work.

--->Must be from outside the US, we would date it 03/19 ;), This antidepressant is said to have a faster onset of action than others. My previous post above lists the countries it is available in. You should NOT take **mirtazapine** & clonidine at the same time (ask your doc how many days you should be off it-less than a week probably). Atenolol for a big speech or event if still needed should be ok but speak with your doc.

Alpha 2-adrenergic mechanism in menopausal **hot** flushes.

Obstet Gynecol 1990 Oct;76(4):573-8 (ISSN: 0029-7844)

Freedman RR; Woodward S; Sabharwal SC
Lafayette Clinic, Detroit, Michigan.

It has been hypothesized that **hot flushes are triggered within the hypothalamus by alpha 2-adrenergic receptors on noradrenergic neurons**. We administered intravenous ***clonidine (an alpha***

2-adrenergic agonist) and ***yohimbine (an alpha 2-adrenergic antagonist)*** to ***nine*** menopausal women with **hot flushes** and to ***an asymptomatic comparison group***. **Hot** flushes were defined objectively by skin conductance responses recorded from the sternum; finger temperature recordings and symptom reports were also evaluated. The subjects were prescreened using ambulatory skin conductance monitoring. *A significantly greater number of hot flushes occurred during yohimbine sessions than in corresponding placebo sessions (six versus zero).* Clonidine *significantly increased the amount of peripheral heating needed to provoke a hot flush (40.6 versus 33.6 minutes) and reduced the number of hot flushes that did occur (two versus eight).* No hot flushes occurred in the asymptomatic women. **These findings support the role of a central alpha 2-adrenergic mechanism in the initiation of hot flushes.**

Major Subject Heading(s)	Minor Subject Heading(s)	CAS Registry / EC Numbers
• Climacteric [physiology] • **Clonidine** [diagnostic use] • Hypothalamus [physiology] • Receptors, Adrenergic, alpha [physiology] • Yohimbine [diagnostic use]	• Adult • Climacteric [drug effects] • Galvanic Skin Response [physiology] • Middle Age • Receptors, Adrenergic, alpha [drug effects] • Skin Temperature [physiology] • Time Factors	• 0 (Receptors, Adrenergic, alpha) • 146-48-5 (Yohimbine) • 4205-90-7 (**Clonidine**)

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CLINICAL PHARMACOLOGY OF **MIRTAZAPINE**

Pharmacodynamics

Evidence gathered in preclinical studies suggests that **mirtazapine** enhances central noradrenergic and serotonergic activity. These studies have shown that **mirtazapine** acts as an **antagonist at central presynaptic a2 adrenergic inhibitory autoreceptors and heteroreceptors**, an action that is postulated to result in an increase in central noradrenergic and serotonergic activity.

Mirtazapine is a potent antagonist of 5-HT2 and 5-HT3 receptors. **Mirtazapine** has no significant affinity for the 5-HT1A and 5-HT1B receptors. **Mirtazapine** is a potent antagonist of histamine (Hi) receptors, a property that may explain its prominent sedative effects.

Mirtazapine is a moderate peripheral a1 adrenergic antagonist, a property that may explain the occasional orthostatic hypotension reported in association with its use.

Mirtazapine is a moderate antagonist at muscarinic receptors, a property that may explain the relatively low incidence of anticholinergic side effects associated with its use

Pain:

Brannon GE, Stone KD. Related Articles

The use of **mirtazapine** in a patient with chronic pain.
J Pain Symptom Manage. 1999 Nov;18(5):382-5.
PMID: 10584463 [PubMed - indexed for MEDLINE]

Craniofacial flushing pain:

Nutt D, Law J. Related Articles

Treatment of cluster **headache** with **mirtazapine**.
Headache. 1999 Sep;39(8):586-7. No abstract available.
PMID: 11279976 [PubMed - indexed for MEDLINE]

*The antidepressant **mirtazapine** successfully treats refractory cluster **headache**:*
Researchers from the UK report the case of a 56 year old man who had an 11 year history of cluster **headache** which had proven refractory to treatment with calcium antagonists, lithium, dexamethasone, prednisolone and sumatriptan. However soon after starting a 6 week course of **mirtazapine** 30mg daily the patient experienced a rapid reduction in the number and severity of attacks.
Nutt. D et al. **Headache** 39: 586-587 Per Inpharma 1999; 1215: 13 (27th Nov).

Lessons From Cluster Headaches:

http://www.emedicine.com/NEURO/topic517.htm -*Pathophysiology and Treatment of Migraine and Related **Headache** here*- "Cluster **headache** is an extremely severe, unilateral, orbital or supraorbital pain associated with ipsilateral facial autonomic symptoms. Pain also may radiate to the back of the neck, suboccipital area, and along the carotid artery. Pain often is boring in nature, lasts from 15 minutes to 4 hours, and typically, patient is awakened in the middle of the night with the **headache**. Tenderness of the temporal artery, facial flushing, and elevated skin temperature on the ipsilateral side have been reported."

&

http://www.emedicine.com/NEURO/topic70.htm -*Cluster **Headache** from Neurology/**Headache** And Pain here*-

Cluster **Headache** (CH): Synonyms, Key Words, and Related Terms: Bing-Horton syndrome, histaminic cephalalgia, cluster migraine, **paroxysmal nocturnal cephalalgia, red migraine, erythromelalgia of the head**, sphenopalatine neuralgia, migrainous neuralgia

"The pathophysiology of CH is not understood entirely. Its typical periodicity has been attributed to hypothalamic (particularly suprachiasmatic nuclei) hormonal influences. CH pain is thought to be generated at the level of the pericarotid/cavernous sinus complex. This region receives sympathetic and parasympathetic input from the brain stem, possibly mediating occurrence of autonomic phenomena during an attack. The exact roles in CH of immunologic and vasoregulatory factors, as well as the influence of hypoxemia and hypocapnia, are still controversial...

- The association of prominent autonomic phenomena is a hallmark of CH. Such signs include ipsilateral nasal congestion and rhinorrhea, lacrimation, conjunctival hyperemia, facial diaphoresis, palpebral edema, and complete or partial Horner syndrome (which may persist between attacks). Tachycardia is a frequent finding.

- A distinctive CH face is described as follows: leonine facial appearance, multifurrowed and thickened skin with prominent folds, a broad chin, vertical forehead creases, and nasal telangiectasias."

Reported Treatments: Abortive: High-flow oxygen; Acute: Ergot alkaloids; Prophylactic agents: intranasal capsaicin, intranasal lidocaine, calcium channel blockers-Verapamil, clonidine, beta-blockers, lithium, baclofen, melatonin, methylergonovine maleate, leuprolide, valproate, topiramate, **Mirtazapine**; short term steroids. Drug resistance-surgical: Radiofrequency trigeminal rhizotomy.

*The antidepressant **mirtazapine** successfully treats refractory cluster **headache**:*
Researchers from the UK report the case of a 56 year old man who had an 11 year history of cluster **headache** which had proven refractory to treatment with calcium antagonists, lithium, dexamethasone, prednisolone and sumatriptan. However soon after starting a 6 week course of **mirtazapine** 30mg daily the patient experienced a rapid reduction in the number and severity of attacks.
Nutt. D et al. **Headache** 39: 586-587 Per Inpharma 1999; 1215: 13 (27th Nov).

***Warnings**: The information above is provided for educational purposes and may not be construed as a medical prescription or as a substitute for the advice of your physicians.*

L3 ANSWER 14 OF 15 MEDLINE
ACCESSION NUMBER: 96047426 MEDLINE
DOCUMENT NUMBER: 96047426 PubMed ID: 7555617
TITLE: Comparison ketoprofen, **ibuprofen** and naproxen sodium in the treatment of **tension-type headache**.
AUTHOR: Lange R; Lentz R
CORPORATE SOURCE: Bayer AG, BG Consumer Care, Leverkusen, Germany.
SOURCE: DRUGS UNDER EXPERIMENTAL AND CLINICAL RESEARCH, (1995) 21 (3) 89-96.
Journal code: 7802135. ISSN: 0378-6501.
PUB. COUNTRY: Switzerland
DOCUMENT TYPE: (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(MULTICENTER STUDY)
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LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199511
ENTRY DATE: Entered STN: 19951227
Last Updated on STN: 19951227
Entered Medline: 19951114

AB The safety and efficacy of treatment of **tension-type headache** with either ketoprofen or **ibuprofen** and naproxen sodium were evaluated in a prospective, randomized, double-blind parallel-group-study in 345 subjects. All patients were valid for evaluation of efficacy and safety. Headache pain intensity and pain relief were measured on categorical verbal scales 30, 45, 60, 120, 180 and 240 min after ingestion of a single dose of 12.5 mg or 25 mg ketoprofen, 200 mg **ibuprofen** and 275 mg naproxen sodium. At no time in four hours observation the efficacy of the four treatments differed, neither in pain intensity difference nor in the pain relief scale. A statistical comparison test was performed only once analysing the primary efficacy variable, the sum of pain intensity differences. There was no statistically significant difference among all treatments in this respect. The results of this clearly indicate that ketoprofen in a dosage of 12.5 or 25 mg, compared to 200 mg **ibuprofen** and 275 mg naproxen sodium, is an effective and safe treatment in **tension-type headache**.

ACCESSION NUMBER: 2001189167 MEDLINE
DOCUMENT NUMBER: 21175210 PubMed ID: 11279976
TITLE: Treatment of cluster **headache** with **mirtazapine**.
AUTHOR: Nutt D; Law J
SOURCE: HEADACHE, (1999 Sep) 39 (8) 586-7.
Journal code: 2985091R. ISSN: 0017-8748.
PUB. COUNTRY: United States
DOCUMENT TYPE: Letter
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Entered Medline: 20010419

L1 ANSWER 5 OF 9 MEDLINE
ACCESSION NUMBER: 2000221909 MEDLINE
DOCUMENT NUMBER: 20221909 PubMed ID: 10749956
TITLE: Use of **mirtazapine** as prophylactic treatment for migraine **headache**.
AUTHOR: Brannon G E; Rolland P D; Gary J M
SOURCE: PSYCHOSOMATICS, (2000 Mar-Apr) 41 (2) 153-4.
Journal code: 0376506. ISSN: 0033-3182.
PUB. COUNTRY: United States
DOCUMENT TYPE: Letter
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Pain Management in the Elderly: Use of Psychopharmacologic Agents

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Chronic pain disorders are common among the elderly. These disorders can re in significant physical disability, social isolation, and emotional sequelae. Altho traditional approaches to pain management (eg, anti-inflammatory agents and opiate analgesics) have been widely advocated for use in a number of chronic p conditions, the elderly are often undertreated for pain. This situation is in part attributable to fears related to risks associated with the use of conventional analgesics. This article reports on emerging evidence focusing on the utility of number of psychopharmacologic agents available for use in chronic pain disor These agents can mitigate pain and comorbid emotional difficulties that can accompany or exacerbate the pain experience. Furtherresearch will be needed

assess the efficacy and safety of these agents among the elderly.
(*Annals of Long-Term Care: Clinical Care and Aging* 2002;10[2]:37-45)

Introduction

Increasing attention has been directed toward the issues of pain management. This in has been mobilized by the efforts of organizations such as Compassion In Dying Federation, which educate the public regarding pain management; increasing public awareness; medical societies; Joint Commission on Accreditation of Healthcare Organizations standards; and recently, the legal system.

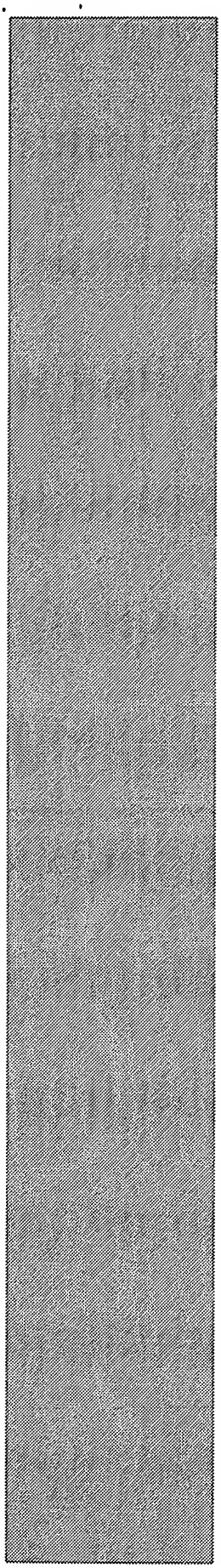
Chronic pain states are prevalent among the elderly. Older individuals are prone t multiple medical conditions predisposing them to pain. They are also very likely to experience pain from terminal medical conditions. [1,2] Estimates suggest that rates of chronic pain among elderly persons are twice those of younger individuals.[3] Among community samples, 20-50% of older persons experience chronic pain;[3] in long-term settings, estimates suggest higher rates approaching 45-80%.[4-7] Common disorders contributing to chronic pain include arthritis, cancer, diabetic neuropathy, herpes zos and osteoporosis.[8,9]

Unfortunately, pain is often poorly recognized and poorly treated among the elderly.[5,10,11] Reasons include poor recognition of symptoms, inadequate time spent evaluating patients, failure to inquire about pain symptoms, inadequate trials of medications to relieve pain, concerns regarding medication adverse effects, and addi fears. The distress resulting from pain may be mislabeled as an emotional disturbanc depression or anxiety. Ascertaining that the patient has pain can be further hindered cognitive deficits and dementia.[5] Nonetheless, pain continues to be pervasive, and it interferes with adaptive functioning, interpersonal functioning, and maintaining quali life.

Pain management has received increasing legal attention. A physician was found of elder abuse based on the premise that he inadequately treated a patient's pain befo patient's death.[12] In a similar action, the Oregon Board of Medical Examiners sanct one of its own members for negligence—ie, the failure to meet the standard of care relates to inadequate pain management.[13] These cases illustrate that external pressur increasing to ensure that physicians become knowledgeable about effective pain management. Consultation with pain management specialists is warranted in particul difficult cases.

Chronic pain can be categorized as nociceptive, neuropathic, or psychogenic (Ta The pain classifications differ in their characteristics and responsiveness to varying ty of treatment interventions.[14] For example, nociceptive pain responds to anti-inflamm agents and opiate analgesics; neuropathic pain responds to antidepressants, anticonvulsants, and possibly neuroleptics. Effective treatment is targeted to underly pain mechanisms.

Table I



Chronic pain is often accompanied by psychological, social, and functional morbi The elderly with depression and anxiety report pain more frequently, and report mor complaints, than nondepressed elderly people.[15,16] Severe emotional distress is likel arise from chronic, poorly treated, and unremitting pain. One drawback of pain classifications such as those outlined in Table I is that they fail to recognize the recip relationship between physiologic and psychological components of pain. Instead, the implication is that chronic pain is either physiologic or psychological in origin.

This article will discuss some of the possible psychopharmacologic approaches to management of pain in the older patient. The recommendations related to the use of conventional analgesics (eg, opiates) among older patients have been described elsewhere.[17] Whereas most of the classes of medications discussed here are employe neuropathic and psychogenic pain, it should be clear that these agents can also be

employed for patients in whom psychological variables impact upon and/or result fro pain experience (even nociceptive types), contribute to deconditioning and disability complicate the functional adaptations that should arise with treatment.

Unfortunately, older patients are often excluded from studies assessing various medication effects in pain reduction. Often, an attempt is made in clinical trials to av the influences of other medical conditions or drug interactions with coadministered medications. Therefore, most of the literature derived from studies employing psychotropic agents has largely focused on diverse patient populations, not exclusiv elderly. Nonetheless, the psychopharmacologic agents described below may offer re older patients with chronic pain. General guidelines for employing such agents are summarized in Table II.

Table II

Antidepressants

Tricyclic antidepressants (TCAs) have long been used for the treatment of chronic neuropathic pain and have demonstrated efficacy in such conditions as painful diabet neuropathy, postherpetic neuralgia, and complex regional pain syndrome (CRPS, for referred to as *reflex sympathetic dystrophy*).[18-23] They are also effective for fibromy psychogenic pain syndromes, and **tension headache**, and for prophylaxis of migrain Thus, there may be a role for TCAs among the elderly, who are likely to suffer from chronic painful conditions.

The analgesic effects of TCAs appear to be independent of any antidepressant eff TCAs have been shown to be effective in patients with chronic pain who do not hav comorbid depression.[25] Doses required for pain relief/reduction are lower than dose required for antidepressant effects.[26] Pain-mitigating doses that are less likely to pro adverse effects can be employed in older patients.

There are pharmacologic differences among TCAs as to selectivity for neurotransmitters. Some have broader aspects of activity—eg, affecting norepinephr and serotonin—while others tend to be more selective for either neurotransmitter. T efficacy of TCAs appears to be related to reuptake inhibition of central nervous syst (CNS) norepinephrine (NE) and serotonin (5-HT). Both of these neurotransmitters a involved in supraspinal and spinal modulator pathways impacting upon pain transmis from the periphery. TCAs with a broader spectrum of activity encompassing both N 5-HT may have more analgesic efficacy than those that are more selective (eg, highe 5-HT selectivity).[21] Thus, the effectiveness of agents such as amitriptyline and imipr appears to be greater than that of the more selective TCAs (eg, desipramine and clomipramine).

The efficacy of TCAs in a variety of chronic pain disorders has been assessed in 3 double-blind studies.[20] Older subjects were included in some of these studies. Howe specific findings of efficacy—eg, among elders as compared with younger patients— not described. A meta-analysis of these studies allowed for estimation of effect sizes Seventy-four percent reported a reduction in pain levels as compared with placebo.[2] Despite the lack of study in homogeneous groups of older patients, data derived from broad range of adult subjects have nonetheless been extrapolated to the treatment of patients.

The utility of TCAs is limited by their side effects. These include dry mouth, constipation, blurred vision, tachycardia, urinary retention, and delirium. The alpha-adrenergic effects of TCAs may produce orthostatic hypotension. Sedation an weight gain may result from influences on histamine.

Absolute contraindications to TCA use include closed-angle glaucoma, acute myocardial infarction, and cardiac arrhythmia. Relative contraindications include ben prostatic hypertrophy and poorly controlled seizure disorder. Prior to a trial with the agents, it is prudent to obtain an electrocardiogram to determine whether cardiac rhy abnormalities would preclude TCA use.[27]

The selection of the TCA to employ should be based upon analgesic efficacy and effects. Amitriptyline and imipramine may be particularly sedating. Desipramine is th least likely to produce anticholinergic effects, while nortriptyline is the least apt to produce orthostatic hypotension.[27]

These agents should be initiated at low doses (eg, amitriptyline, 10-25 mg daily). doses should be increased slowly as tolerated to maximize analgesic efficacy. If thes

agents are administered at night, their sedative effects may facilitate sleep. Patients w comorbid depression may require higher antidepressant doses.

Suicide risk is increased with age, particularly among men, and in individuals wit chronic pain and terminal illnesses.[28] Caution is required when prescribing TCAs be these agents are lethal when taken in overdose. Therefore, assessment of suicidal ide intent, and plans is warranted. TCA use is not precluded, even for patients at risk fo suicide. These patients should be followed up frequently (eg, weekly) and given only enough of the medication to last until the next visit. Enlisting the support of family members or others to dispense medication and monitor its use is desirable.

Selective Serotonin Reuptake Inhibitors

Because of the greater tolerability of side effects and relative safety in overdose, the selective serotonin reuptake inhibitors (SSRIs) have been investigated as adjuvant th for pain. Few adequately controlled studies have been conducted to confirm the effic of SSRIs as analgesic agents. The literature on SSRI effectiveness is also limited by small sample sizes and small dosage ranges employed in such studies.[29] Still fewer s have dealt with the analgesic effectiveness in the aged.

SSRIs found to be effective for one type of pain do not necessarily have efficacy other types. For example, fluoxetine may be useful for chronic daily **tension** headach but may not be effective for diabetic neuropathy.[30,31] The effectiveness of one SSRI necessarily generalizable to other SSRIs. Paroxetine appears to be effective for neuropathic pain, but fluoxetine does not.[21,32,33]

The reduced efficacy of SSRIs as compared with TCAs may be related to their serotonin selectivity. As noted previously, those TCAs with broader spectra of neurotransmitter activity, including NE and 5-HT, fared better than those with more selective 5-HT activity.[21] It is possible, therefore, that the more selective 5-HT activ the SSRIs may limit their utility in pain reduction.

As with TCAs, SSRIs are initiated at the lowest possible doses. The doses are increased slowly as tolerated and as warranted by the need for analgesic and/or antidepressant or anxiolytic efficacy. Side effects associated with their use include gastrointestinal (GI) effects (eg, nausea, vomiting), insomnia or sedation, tremors, a sexual dysfunction.[27]

Other Antidepressants

Other antidepressants have also been studied for their use in chronic pain. Both venlafaxine and bupropion—which have a broad spectrum of activity including effec NE, 5-HT, and dopamine—display some promise.[34] Venlafaxine has been employed treat fibromyalgia, chronic **headache**, and neuropathic pain.[35,36] Anecdotal evidenc suggested that venlafaxine may be useful in managing pain associated with stroke, postherpetic neuralgia, and other neuropathies.[37] Bupropion has been used to addre pain related to peripheral neuropathy.[38] Unlike TCAs, these agents may be especial useful in the elderly due to the lack of cardiac side effects, fewer anticholinergic side effects, and fewer risks of drug interactions. There is a risk of seizure associated wit higher doses of bupropion; venlafaxine may be associated with nervousness, insomn weight loss, and elevations in diastolic blood pressure.[27] If TCAs cause unacceptabl effects, these other agents may prove to be viable alternatives for older patients.

There are a number of additional antidepressants with prominent 5-HT effects th

have utility in depressive disorders—eg, trazodone, nefazodone, and mirtazapine. O one double-blind study[39] involving nefazodone and one case report[40] involving mirtazapine in pain reduction exist in the literature. Clinical trials investigating the r of these antidepressants are warranted. While two double-blind studies demonstrated efficacy of trazodone in diabetic neuropathy and pain resulting from deafferentation nerves,[41,42] the effects on patients with headache, fibromyalgia, rheumatoid arthriti chronic low back pain are less promising.[29]

Trazodone may facilitate sleep. The analgesic properties of trazodone appear to b independent of its sedative effects.[29] Orthostatic hypotension can occur, particularly higher doses of trazodone are employed. Men may experience painful priapism requ emergency interventions. [27] Dosing should be kept to a minimum, and increased onl gradually, to reduce the risk of adverse effects.

Antiepileptic Drugs

Antiepileptic drugs (AEDs) historically have demonstrated efficacy in neuropathic pain—eg, trigeminal neuralgia, postherpetic neuralgia, painful diabetic neuropathy, a CRPS.[43] Their analgesic effect is presumed to be related to the slowing of periphera nerve conduction in primary afferent fibers, thereby dampening the painful sensory information relayed to the CNS. AEDs influence gamma-aminobutyric acid (GABA) activity, which is responsible for inhibiting pain processes within the spinal cord and They also inhibit the production of pain-promoting neurotransmitters. [44]

Because of the differences in the pain-relieving effects of AEDs and antidepressa AEDs are viable alternatives for patients with pain that persists despite optimal antidepressant use or for whom antidepressants prove intolerable. Antidepressants a AEDs may be administered simultaneously because the analgesic mechanisms of the classes of agents complement each other. When they are coadministered, lower dose the antidepressant and/or the AED are possible, resulting in fewer adverse effects.

Because of their mood-stabilizing effects,[45] AEDs may be useful among the elde psychiatric comorbid conditions (eg, impulsivity arising from dementia, mood lability dementia or bipolar disorder). Adverse effects common with AEDs include sedation fatigue, GI side effects, and motor side effects.

Gabapentin has received approval from the U.S. Food and Drug Administration (for use in the treatment of neuropathic pain. This drug offers numerous advantages o other available AEDs. It is unlikely to produce serious side effects associated with th of other anticonvulsants—eg, hyponatremia and neutropenia connected with carbamazepine (CBZ) use or hepatic effects associated with valproate use. Patients t gabapentin do not require serum drug, hematologic, electrolyte, or hepatic enzyme monitoring as is often required with other AEDs. The most common adverse events reported with the use of gabapentin are somnolence, dizziness, ataxia, tremor, fatigu nystagmus. Because this agent is excreted unchanged from the kidneys, dose reducti are required for patients who have compromised renal functioning or who require dialysis.[46-48]

CBZ is approved by the FDA for use in trigeminal neuralgia; [49] valproate has bee indicated for migraine prophylaxis.[50] Along with phenytoin, CBZ and valproate hav shown to be efficacious in chronic neuropathic pain.[44,49,51-57] Issues related to use, dosing, adverse effects, and drug interactions for these and other AEDs are discusse detail elsewhere.[44,45,49]

Emerging evidence suggests the potential role of newer AEDs, such as lamotrigin oxcarbazepine, in pain control.[58] Although these agents have demonstrated some pr with regard to potential utility in neuropathic states,[59-61] their utility and safety amo elderly require further investigation. They may offer better tolerability over other AE (eg, CBZ) and may be useful in patients with pain that is poorly responsive to other agents.

As with most psychopharmacologic agents, initial doses should be low; doses sho be increased gradually, with monitoring for intolerance or adverse events. Gabapent be initiated at 300 mg/day and increased slowly as tolerated until pain relief is achiev

Antihistamines

A variety of antihistamines have been employed with some efficacy in a number of p disorders.[62] Histamines have been implicated in a number of pain states (eg, **headac** and inflammatory pains) by facilitating inflammatory processes such as prostaglandin production. Antihistamine effects, therefore, would be expected to reduce pain medi by inflammatory processes. Furthermore, antihistamine effects appear to augment op receptor binding of opioid analgesics.[63]

In the elderly, antihistamines might be considered as augmenting agents to furthe effects of other analgesics (eg, opiates) or used as solitary agents. Used alone, antihistamines such as hydroxyzine appear to have a ceiling, doses beyond which fai produce enhanced analgesia. These drugs are fairly well-tolerated, with little in the w respiratory or GI side effects. These agents can be sedating, however, and can increa appetite.

Diphenhydramine and hydroxyzine have been shown to have clinical efficacy with regard to pain relief.[63] Additionally, these agents may be particularly useful in patien given their sedative, antiemetic, and anxiolytic properties.

Antihistamines should be initiated at low doses (eg, hydroxyzine, 25 mg/daily). Increasing the dosage should proceed slowly as warranted and as tolerated to addres pain, sleep, and other conditions.

Benzodiazepines and Anxiolytics

Benzodiazepines can be effective in mitigating pain arising from muscle spasm.[64] Th of benzodiazepines may be considered in patients with fibromyalgia and other musculoskeletal disorders. The use of these drugs has to be undertaken cautiously b these agents can contribute to excess sedation, gait instability, and falls, as well as m impairments. Patients with anxiety are prone to heightened muscle **tension** that can exacerbate musculoskeletal pain. Benzodiazepines may be effective in mitigating associated distress, thus preventing spasms, reducing the likelihood of inactivity resu from pain and spasm, and preventing the deconditioning that arises from protracted inactivity.

Clonazepam, a long-acting benzodiazepine, may be effective in patients with neuropathic pain in which allodynia—painful sensations elicited by normally nonnox stimuli (eg, a bed sheet being pulled up along the legs)—appear to be a prominent feature.[65] This drug is also useful for associated insomnia, anxiety, and seizure disor

Buspirone is an anxiolytic agent that differs from benzodiazepines. Unlike benzodiazepines, which exert their anxiolytic effects by means of influencing GABA activity, buspirone does not interact with GABA but mediates its antianxiety effect through the 5-HT_{1A}

receptor. Patients with neuropathic pain have tended to respond unfavorably to busp treatment.[66] However, in patients with severe anxiety that may aggravate pain experiences, a trial of buspirone to mitigate anxiety may be warranted.

Neuroleptics

Limited studies have demonstrated the efficacy of various neuroleptics in chronic pa states. Of these, conventional antipsychotics (eg, fluphenazine) have been found to b useful in certain cases of neuropathic pain.[67] One antipsychotic, methotrimeprazine, demonstrated analgesic activity comparable to low-dose morphine.[68] This agent is u Europe but is not available in the United States. Because of limited data on efficacy side effects, the use of neuroleptics for pain control should probably be confined to t older patient who has delirium and/or psychosis.

Conclusion

There is much that needs to be investigated regarding the management of chronic pa the elderly. It is likely that psychotropics can offer relief for patients, particularly for neuropathic and psychogenic pains. Since mood disturbances (eg, depression and an and other comorbid conditions (eg, sleep disturbances) can complicate the experienc chronic pain, it is likely that psychotropics are useful. Further inquiry will be require establish the efficacy, safety, and tolerability of such agents among the elderly.

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Practice Guidelines

Guidelines on Migraine: Part 5. Recommendations for Specific Prophylactic Drugs

Sharon Scott Morey

The U.S. Headache Consortium guidelines for the treatment of migraine summarize data from clinical studies of various drugs used in preventive therapy of migraine. The analysis included alpha$_2$ agonists, anticonvulsants, antidepressants, beta blockers, calcium channel antagonists, nonsteroidal anti-inflammatory drugs (NSAIDs), serotoninergic agents, hormonal agents, feverfew, magnesium and vitamin B_2 (riboflavin). Members of the consortium graded the quality of the evidence for the use of a particular drug based on the findings from clinical trials. The bulk of the analysis was based on the technical review of the treatment of migraine by the Agency for Healthcare Research and Quality (AHRQ, formerly the Agency for Health Care Policy and Research). *See the accompanying table below* for a comprehensive list of specific drugs and the strength of the evidence for their use in the prophylaxis of migraine.

Summary of Evidence for Specific Drugs for Prophylaxis

The following highlights the findings from clinical studies of specific agents:

- **Alpha$_2$ agonists**--Sixteen trials of clonidine and one trial of guanfacine were reviewed and suggested that alpha$_2$ agonists are minimally and not conclusively efficacious. Three of 11 placebo-controlled trials of clonidine showed a significant difference between placebo and treatment arms, but the magnitude of the effect was small.
- **Anticonvulsants**--Strong support of the efficacy of divalproex and valproate was found in five studies of these agents. The **headache** consortium found that the evidence was weaker in support of the use of other anticonvulsants, such as carbamazepine, clonazepam and gabapentin.
- **Antidepressants**--Clinical studies indicate that amitriptyline is the only antidepressant that has shown fairly consistent efficacy in the prevention of migraine. This agent has also been evaluated more frequently than other antidepressants. One study revealed that fluoxetine was significantly better than placebo in the prevention of migraine, but another study failed to duplicate this finding. A randomized placebo-controlled study, reported in 1998, showed that fluoxetine may be beneficial in the prevention of migraine.
- **Beta blockers**--The AHRQ report on drug therapies for the prevention of migraine included analysis of 74 controlled trials of beta blockers. Propranolol was investigated in 46 studies and metoprolol in 14 studies. The consortium found consistent evidence for the efficacy of propranolol, 120 to 240 mg daily, in the prevention of migraine attacks. Studies indicate that beta blockers with intrinsic sympathomimetic activity are ineffective for preventing migraine.
- **Calcium channel antagonists**--The review included 45 controlled trials of calcium channel antagonists, including 11 trials of nimodipine, five trials of nifedipine, three trials of verapamil and one trial of nicardipine. Three placebo-controlled trials of nimodipine showed no significant difference between the active agent and placebo, but two trials showed large and statistically significant differences in favor of nimodipine. In two of three placebo-controlled trials of verapamil, significant differences were found with the calcium channel blocker, but the relevance of the findings is uncertain because of high dropout rates in the two studies. In a placebo-controlled trial that included a propranolol arm, no significant differences in the effects on **headache** frequency were noted between verapamil and propranolol.
- **NSAIDs**--The AHRQ review included 23 controlled trials of 11 different NSAIDs. A meta-analysis of five placebo-controlled trials of naproxen or naproxen sodium suggests a modest but statistically significant effect on **headache** index or frequency. In several studies that compared NSAIDs with propranolol and metoprolol, no differences between these agents were found.
- **Serotoninergic agents**--The review included 13 controlled trials of ergot derivatives. According to the U.S. **Headache** Consortium, the evidence is insufficient for the efficacy of ergotamine or the combination of ergotamine, caffeine, butalbital and belladonna alkaloids (Cafergot compound) in the prevention of migraine. The guidelines also state that the usefulness of methysergide is now limited because of its association with retroperitoneal and retropleural fibrosis.
- **Hormone therapy**--The review included six controlled trials on the use of estrogens and/or progestogens for the prevention of migraine. Two placebo-controlled trials of estradiol, administered premenstrually as a gel or patch, suggest that a relatively high dosage (1.5 mg per day of the gel form) may be effective in women whose migraines

are associated with their menstrual cycle. Evidence does not point to a benefit in patients whose migraines are not related to the menstrual cycle.

- **Feverfew**--Three trials of feverfew suggest that this herbal remedy may have an effect on migraine. One trial of a group of patients who used feverfew showed that withdrawal of the herb was followed by a statistically significant increase in **headache** frequency. Another study of patients who had never used feverfew revealed a statistically significant difference between the feverfew group and the placebo group. In a double-blind, randomized, crossover trial, feverfew was found to be associated with a significant reduction in pain intensity and other symptoms such as nausea, vomiting, photophobia and phonophobia.
- **Vitamins and minerals**--Two studies showed benefits of magnesium over placebo, whereas a third study failed to show any benefit. In one study of high-dose (400 mg) vitamin B_2 (riboflavin), a significant benefit was noted three and four months after initiation of vitamin B_2 supplementation.

Summary of the Evidence for Efficacy of Drugs Used in the Prevention of Migraine

Drug (dosages tested)	Quality of evidence*	Scientific effect¶	Clinical impression of effect¥	Adverse effects	Comments
Alpha$_2$ agonists					
Clonidine (0.05 to 0.225 mg per day)	B	0	0	Occasional to frequent	CNS adverse events common; overwhelming evidence demonstrates no clinical benefit for prevention of migraine.
Guanfacine (0.5 to 1 mg per day)	B	+	Unknown	Infrequent (low dose)	Limited evidence indicating superiority of 1-mg dose over 0.5-mg dose. Limited value in patients with coexistent hypertension
Anticonvulsants					
					Most common adverse events include vertigo, giddiness and drowsiness. Not

Carbamazepine (600 mg per day)	B	++	0	Occasional to frequent	recommended based on limited evidence of efficacy. High incidence of adverse events and methodologic concerns.
Divalproex sodium (500 to 1,500 mg per day), sodium valproate (800 to 1,500 mg per day)	A	+++	+++	Occasional to frequent	Some adverse events more than occasionally occur, including nausea, asthenia and somnolence, when higher doses are used. Other side effects include weight gain, hair loss, tremor, neural tube defects and teratogenic potential. Recommended for patients with prolonged oratypical migraine aura. Not recommended for patients with liver disease. Safety and tolerability profiles specifically in migraineurs appear similar to those in patients with other disorders.
Gabapentin (900 to 2,400 mg per day)	B	++	++	Occasional to frequent	Limited available data (two trials reported as abstracts) indicate benefit at doses ranging from 900 to 2,400 mg.
					Occasional CNS adverse events

Tiagabine and topiramate (doses not given)	C	Unknown	++	Occasional	with both agents; kidney stones and weight loss with topiramate; sedation could occur at doses of topiramate required to achieve efficacy
Antidepressants					
Amitriptyline (25 to 150 mg per day)	A	+++	+++	Frequent	Drowsiness, weight gain and anticholinergic adverse events are common; long-term weight gain can be troublesome. Particularly useful in patients with migraine and **tension headache** and in patients with depression. Risk of drug interaction between cisapride and amitriptyline. May lower seizure threshold in patients with frequent seizures.
Nortriptyline (doses not given)	C	Unknown	+++	Frequent	Better tolerated than amitriptyline
Protriptyline (doses not given)	C	Unknown	++	Frequent	Nonsedating and not as frequently associated with weight gain as other tricyclic antidepressants
Doxepin, imipramine (doses not given)	C	Unknown	+	Frequent	See prescribing information for adverse events
					Insomnia, fatigue, tremor and stomach pain are the more common

Fluoxetine (20 mg every other day to 40 mg per day)	B	+	+	Occasional	adverse events. Consider use in patients with coexistent depression. SSRIs rarely interact with serotonin receptor antagonists.
Fluvoxamine, paroxetine, sertraline(doses not given)	C	Unknown	+	Occasional	See prescribing information and text above
Phenelzine (doses not given)	C	Unknown	+++	Frequent	Requires complex management with special dietary restrictions. High potential for drug-drug interactions. May be helpful in patients with coexistent depression or when antidepressants from other classes fail.
Bupropion, mirtazapine, trazodone, venlafaxine (doses not given)	C	Unknown	+	Occasional	May be used in patients with coexistent depression or trazodone, venlafaxine anxiety
Beta blockers					
Atenolol (100 mg per day)	B	++	++	Infrequent	Adverse events include tiredness, fatigue and dizziness.
					May not be accepted by active patients such as athletes. Particularly helpful in patients with coexistent anxiety or panic

Metoprolol (50 to 300 mg per day)	B	++	+++	Infrequent	attacks and essential tremors (propranolol). When propranolol is used in conjunction with rizatriptan, a lower dose of rizatriptan should be given. Should not be used in patients with coexistent asthma, cardiac insufficiency or Raynaud's disease. May exacerbate depression
Nadolol (80 to 240 mg per day)	B	+	+++	Infrequent	As above
Propranolol (40 to 240 mg per day)	A	++	+++	Infrequent	As above
Timolol (20 to 30 mg per day)	A	+++	++	Infrequent	As above
Calcium channel antagonists					
Diltiazem (doses not given)	C	Unknown	0	Occasional	Tolerability similar to others in class
Nimodipine (60 to 120 mg per day)	B	+	+	Occasional	Abdominal discomfort common. Cost may be prohibitive.
Verapamil (240 mg per day)	B	+	+	Occasional	Constipation common. Do not use if conduction block is present. Alternative to beta blockers in athletes. Recommended in patients with coexistent stroke or for prolonged or atypical migraine aura

NSAIDs

Aspirin (325 mg every other day, 1,300 mg per day); fenoprofen (600 to 1,800 mg per day); flurbiprofen (200 mg per day); mefenamic acid (1,500 mg per day)	B	+	+	Infrequent	Common adverse events include abdominal discomfort, gastritis and occult GI bleeding. May be useful in patients with arthritis. Consider aspirin in patients with coexistent stroke.
Aspirin + dipyridamole (975 to 1,300 mg + 75 mg per day)	B	+	Unknown	Infrequent	As above
Ibuprofen (doses not given)	C	Unknown	+	Infrequent	As above
Ketoprofen (150 mg per day)	B	++	+	Infrequent	As above
Naproxen (500 mg per day); naproxen sodium (1,100 mg per day)	B	++	++	Infrequent	As above
Serotonin antagonists					
Cyproheptadine (doses not given)	C	Unknown	+	Frequent	Used in pediatric migraine. Weight gain and fatigue are common adverse events.
Ergotamine + caffeine + butalbital + belladonna alkaloids (2 capsules per day for three days before, during and two days after menses)	B	++	++	Occassional	Cafergot compound twice daily during the perimenstrual period was shown to reduce **headache** frequency for migraine associated with menses. Limited information available regarding adverse events associated with treatment for menses-related migraine.

Methylergonovine (methylergometrine; doses not given)	C	Unknown	+	Frequent	May be used in hormonally influenced migraine.
Methysergide (2 to 10 mg per day based on body weight)	A	+++	+++	Frequent	GI adverse events common. Serious adverse events include retroperitoneal and retropleural fibrosis, which may be associated with uninterrupted use. Triptans and ergotamines should be used with caution.
Other agents					
Estradiol (1.5 mg per day for 7 days, gel)	B	++	++	Infrequent	Short-term prevention of migraine associated with menses. Adequate dose required.
Feverfew (50 to ~82 mg per day)	B	++	+	Infrequent	Mild adverse events. Withdrawal of feverfew may be associated with increased frequency of headaches.
Magnesium (400 to 600 mg per day)	B	+	+	Infrequent	Use of nonchelated formulation is associated with significant diarrhea at clinically effective doses. May be useful in patients with PMS.
Vitamin B_2 (400 mg per day)	B	+++	++	Infrequent	Rare adverse events; no known interaction with other drugs.

CNS = central nervous system; SSRIs = selective serotonin reuptake inhibitors; NSAIDs = nonsteroidal anti-inflammatory drugs; GI = gastrointestinal; PMS = premenstrual syndrome.

*--Quality of the evidence is classified as follows: Grade A signifies evidence from multiple well-designed randomized clinical trials, directly relevant to the recommendation, yielded a consistent pattern of findings. Grade B signifies some evidence from randomized clinical trials supported the recommendation, but the scientific support was not optimal. For instance, few randomized trials existed, the trials that did exist were somewhat inconsistent or the trials were not directly relevant to the recommendation. An example of the last point would be the case in which trials were conducted using a study group that differed from the target group for the recommendation. Grade C signifies that the U.S. Headache Consortium achieved consensus on the recommendation in the absence of relevant randomized controlled trials.

¶--Scientific effect is classified as follows: 0 = the drug is ineffective or harmful; + = the effect is either not statistically or not clinically significant (i.e., less than the minimal clinically significant benefit); ++ = the effect of the drug is statistically significant and exceeds the minimal clinically significant benefit; +++ = the effect is statistically significant and far exceeds the minimal clinically significant benefit.

¥--Clinical impression of effect is classified as follows: 0 = ineffective, most patients have no improvement; + = somewhat effective, few people have clinically significant improvement; ++ = effective, some people have clinically significant improvement; +++ = very effective, most people have clinically significant improvement.

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The treatment recommendations for nonpharmacologic therapies are as follows:

Funding and support for the evidence-based migraine guidelines were provided by Abbott Laboratories, AstraZeneca, Bristol Myers Squibb, Glaxo Wellcome, Merck, Pfizer, Ortho-McNeil and the American Academy of Neurology Education and Research Foundation, along with the seven participant member organizations, which include the American Academy of Family Physicians, the American Academy of Neurology, the American Headache Society, the American College of Emergency Physicians, the American College of Physicians-American Society of Internal Medicine, the American Osteopathic Association and the National Headache Foundation. *

This is the final part of a five-part series summarizing the U.S. Headache Consortium guidelines on migraine. The first part, on the use of diagnostic imaging in nonacute headache, appeared in the October 1 issue of *American Family Physician.* The second part, on the general principles of drug therapy, appeared in the October 15 issue. The third part, on recommendations for specific drugs for acute treatment, appeared in the November 1 issue. The fourth part, on general principles of preventive therapy, appeared in the November 15 issue.

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HEADACHE

THE JOURNAL OF HEAD AND FACE PAIN

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ABSTRACTS

ORGANIC CAUSES OF HEADACHE

Mackenzie RA, Lethlean AK, Shnier R, Blum PW. Chronic intracranial hypotension.

Acute intracranial hypotension can occur following lumbar puncture or a fall, and sometimes spontaneously. Most cases resolve within weeks or months but some require surgical repair of the defect causing leakage of cerebrospinal fluid (CSF). It is conceivable that such leaks could become chronic if the defect is incompletely sealed. We report the case of a 49-year-old male who presented with a 10-month history of headache associated with a leaking thoracic extradural arachnoid cyst. After this was repaired he reported relief not only of his recent headaches but also of chronic alcohol-related headaches. A long-standing anemia resolved and tinnitus/hyperacusis improved. It is suggested that an injury 30 years before may have initiated the leak of CSF resulting in chronic intracranial hypotension.

J Clin Neurosci. 1998;5:457-460.

McAuley JH, Grunewald RA, Scadding JW. Idiopathic spontaneous subdural hemorrhage.

We describe three middle-aged and previously healthy patients in whom idiopathic spontaneous subdural hemorrhage occurred, giving rise to headache with minimal or no neurological signs and resolving with conservative management. Previous reports of this condition describe an associated severe neurological impairment, a poor prognosis, and a necessity for surgical evacuation. Our cases indicate that mild and self-limiting spontaneous subdural hemorrhage may occur and is perhaps underdiagnosed in our patients' age group because it presents non-specifically with headache.

Cephalalgia 1998;18:490-492.

Biousse V, Touboul PJ, DAnglejanChatillon J, Levy C, Schaison M, Bousser MG. Ophthalmologic manifestions of internal carotid artery dissection.

Purpose: To report the ophthalmologic symptoms and signs associated with extracranial internal carotid artery dissection.

Methods: One hundred forty-six consecutive patients with extracranial internal carotid artery dissection were evaluted; 29 were studied retrospectively from 1972 to 1984 and 117 prospectively from 1985 to 1997.

Results: Sixty two percent of patients (91/146) with extra-cranial internal carotid artery dissection had ophthalmologic symptoms or signs that were the presenting symptoms or signs of dissection in 52% (76/146). Forty-four percent (65/146) had painful Horner syndrome, which remained isolated in half the cases (32/65). Twenty eight percent (41/146) had transient monocular visual loss, which was painful in 31 cases, associated with Horner syndrome in 13 cases, and described as "scintillations" or "flashing lights"-often related to postural changes or exposure to bright lights-suggesting acute choroidal hypoperfusion in 23 cases. Four patients had ischemic optic neuropathy; one had diplopia. Among the 76 patients with ophthalmologic symptoms or signs as the presenting features of carotid dissection, a nonreversible ocular or hemispheric stroke later occurred in 27, within a mean of 6.2 days (range, 1 hour to 31 days). Eighteen patients had a stroke within the first week after the onset of neuro-ophthalmic symptoms and signs, and 24 had a stroke within the first 2 weeks.

Conclusion: Ophthalmologic symptoms or signs are frequently associated with and are often the presenting features in internal carotid artery dissection. Painful Horner syndrome or transient monocular visual loss should prompt investigations to diagnose carotid artery dissection and begin early treatment to prevent a devastating ocular or hemispheric stroke.

Comment: The majority of patients with carotid dissection will have ophthalmologic symptoms or signs.

Am J Ophthalmol 1998;126:565-577.

Weinberg JS, Freed DL, Sadock J, Handler M, Wisoff JH, Epstein FJ. Headache and Chiari I malformation in the pediatric population.

There has been disagreement regarding surgical intervention in treating pediatric patients with Chiari I malformation with headache as sole complaint. Therefore, we retrospectively reviewed our experience over a 6-year period, with patients less than 5 years of age (mean = 34.8 months) with radiographically confirmed Chiari I malformation. We identified 7 patients who presented with headaches as their only complaint. The headaches varied in location and severity. All patients were treated with posterior fossa decompression and syringosubarachnoid shunt when indicated. At follow-up, all patients were noted to have rapid clinical improvement (mean = 11.6 weeks) and remain asymptomatic. Our data suggest that patients less than 5 years of age with Chiari I malformation benefit from surgical decompression when presenting with a chief complaint of headache.

Comment: Mild Chiari malformations without positional/exertional short-lasting headache or lower brainstem symptoms should probably be treated medically first. In this series, 7 of 7 children with headache as their only symptom had complete relief following surgery. I have seen 3 adult patients with refractory headache without positional/exertional features and no lower brainstem symptoms who were found to have a Chiari I. Following surgery, there was no significant change in headache frequency or severity. Because of this experience, I am reluctant to recommend surgery when typical features are absent.

Pediat Neurosurg 1998;29:14-18.

Evers S, Husstedt IW. Headache and HIV infection - a systematic review.

The etiology and epidemiology of the different headache types occurring during HIV infection and the changes of preexisting primary headache types during HIV infection are reviewed on the basis of published controlled studies and of own epidemiological studies. Headache during HIV infection may occur as a symptom of aseptic meningitis with an increasing frequency during the stages of infection. This headache is similar to tension-type headache and can be regarded as an HIV-associated headache. Opportunistic infections and neoplasms can lead to headache by inflammatory mechanisms or by increasing intracranial pressure. Antiretroviral treatment can lead to headache as a drug-related side effect. Preexisting migraine decreases in frequency and intensity during the HIV infection whereas preexisting tension-type headache seems to increase. Management of headache during HIV infection is not different from the management in non-infected headache patients, however, an undertreatment of pain in HIV infected patients has been shown. In severe cases, pain treatment should be performed in specialised clinics in order to improve the quality of life as long as possible.

Nervenheilkunde 1998;17:283-289.

Feghali JG, Elowitz EH. Split calvarial graft cranioplasty for the prevention of headache after retrosigmoid resection of acoustic neuromas.

Objective: This study describes the technique and efficacy of split calvarial graft cranioplasty for the reconstruction of retrosigmoid/suboccipital defects following surgery for acoustic neuromas.

Study Design: A prospective study of the technique of split calvarial graft cranioplasty, its postoperative healing, and incidence of postoperative headache. Methods: The technique requires splitting of the craniotomy bone flap into outer and inner table bone grafts, The combination of both bony grafts allows the coverage of a wider area of posterior fossa dura. This technique was used in 18 patients. All patients were followed for a minimum of 6 months. Eleven of 18 patients were followed for 1 year or longer. Four patients had three-dimensional computed tomography of their skull and area of split calvarial bone graft.

Results: One of 18 patients had a persistent disabling headache at 1 year postoperatively. A natural contour of the retrosigmoid area was achieved in all patients. Three-dimensional computed tomography scan, obtained 6 months postoperatively, showed total coverage of the retrosigmoid area and fusion of the bone flap to the surrounding skull.

Conclusion: The technique of split calvarial grafting of posterior fossa defects is a feasible, safe, and effective way of separating the nuchal musculature and posterior fossa dura. The technique also allows the restoration of the contour and bony covering of the retrosigmoid area. The technique is a simple alternative to other types of cranioplasties aimed at reducing the incidence of postoperative headache in patients with acoustic neuromas.

Comment: I have found headache following an occipital approach for acoustic neuromas difficult to treat. The headache is often disabling and refractory to standard headache medications.

Laryngoscope 1998;108:1450-1452.

Hernandez A, DelReal MA, Aguirre M, Vaamonde J, Gudin M, Ibanez R.

Pituitary apoplexy: a transient benign presentation mimicking mild subarachnoid hemorrhage with negative angiography.

We report on a patient who presented with isolated transient headache as the only manifestation of pituitary apoplexy. A high index of suspicion and MRI led to the diagnosis.

Eur J Neurology 1998;5:499-501.

Maghrabi K, Bohlega S. Cyclosporine-induced migraine with severe vomiting causing loss of renal graft. Clin Neurol.

Successful use of cyclosporine in organ transplant can be associated with unwanted side-effects that can affect graft function. We report three kidney transplant recipients in whom severe migraine headache occurred as a side-effect of cyclosporine therapy. This endangered graft survival in all three and eventually led to loss of graft in two.

Neurosurg 1998 ;100(3):224-227.

Christoforidis GA, Mehta BA, Landi JL, Czarnecki EJ, Piaskowski RA. Spontaneous intracranial hypotension: report of four cases and review of the literature.

Spontaneous intracranial hypotension is an unusual syndrome of postural headache and low cerebrospinal fluid pressure without an established cause. We present four cases, analyze those previously reported in the literature, examine the MRI, CT, angiographic and cisternographic finding and discuss the clinical picture, proposed pathophysiologic mechanisms and potential treatment.

Neuroradiology 1998;40:636-643

Linn FHH, Rinkel GJE, Algra A, vanGijn J. Headache characteristics in subarachnid haemorrhage and benign thunderclap headache.

One third of patients with aneurysmal subarachnoid haemorrhage (ASAH) present with headache only. A prompt diagnosis is crucial, but these patients must be distinguished from patients with non-haemorrhagic benign thunderclap headache (BTH). The headache characteristics and associated features at onset in subarachnoid haemorrhage and benign thunderclap headache were studied to delineate the range of early features in these conditions. In this prospective study, one of two observers interviewed 102 patients with acute severe headache by means of a standard questionnaire. The patients were alert on admission and had no focal deficits. ASAH was subsequently diagnosed in 42 patients, non-aneurysmal perimesencephalic haemorrhage (PMH) in 23 patients, and BTH in 37 patients. Headache developed almost instantaneously in 50% of patients with ASAH, 35% of patients with PMH, and 68% of patients with BTH and within 1 to 5 minutes in 19%, 35%, and 19%, respectively. Loss of consciousness was reported in 26% of patients with ASAH, 4% of patients with PMH and 16% of patients with BTH, and transient focal symptoms in 33%, 9%, and 22% respectively. Seizures and double vision had occurred only in ASAH. Vomiting and physical exertion preceding the onset of headache were more frequent in patients with ASAH (69% and 50%) and those with PMH (83% and 39%) than in those with BTH (43% and 22%). Headache developed almost instantaneously in only half the patients with aneurysmal rupture and in two thirds of patients with benign thunderclap headache. In patients with acute severe headache, female sex, the presence of seizures, a history of loss of consciousness or focal symptoms, vomiting, or exertion increases the probability of ASAH, but these characteristics are of limited value in distinguishing ASAH from BTH. Aneurysmal rupture should be considered even if focal signs are absent and

the headache starts within minutes.

Comment: Unexplained sudden severe headache requires a noncontrast CT followed by an LP if the CT scan is normal. While most patients presenting with sudden severe headache (and no deficits) are scanned by emergency physicians at university hospitals, only 50% get a spinal tap. On day 0 the false negative rate for SAH is 2-8%. Non-hemorrhagic disorders that might be missed by CT scan but suggested by CSF examination include herpes simplex encephalitis and sagittal sinus thrombosis (elevated CSF pressure).

J Neurol Neurosurg Psychiatry 1998;65:791-793.

Klein CJ, Nakumura M, Jacobson DR, Lacy MQ, Benson MD, Petersen RC. Transthyretin amyloidosis (serine 44) with headache, hearing loss, and peripheral neuropathy.

A 32-year-old man of Irish descent presented with severe progressive headache and sensorineural hearing loss. MRI/magnetic resonance angiography head scans were normal. A length-dependent sensorimotor peripheral neuropathy with autonomic dysfunction predated these symptoms. Systemic organ involvement and transthyretin (TTR) amyloid immunostaining of bone marrow and fat aspirate were documented. Direct DNA sequencing revealed both the normal TTT (phenylalanine) and a new variant TCT (serine) at position 44 of the TTR gene. This case expands the genotypic and phenotypic variability within TTR amyloidosis.

Neurology 1998;51:1462-1464.

Stollberger C, Finsterer J, Fousek C, Waldenberger FR, Haumer H, Lorenz W. Headache as the initial manifestation of acute aortic dissection type A.

The most common initial symptom of aortic dissection is chest pain. Other initial symptoms include pain in the neck, throat, abdomen and lower back, syncope, paresis, and dyspnea. Headache as the initial symptom of aortic dissection has not been described previously. A 61-year-old woman with a history of migraine and arterial hypertension developed continuous bifrontal headache. Two hours later, right-sided thoracic pain and a diastolic murmur were suggestive of aortic dissection that was confirmed by echocardiography and subsequent surgery. The dissection commenced in the ascending aorta and involved all cervical arteries at the base of the skull. Headache as the initial manifestation of aortic dissection was assumed due to either vessel distension or pericarotid plexus ischemia. Aortic dissection has to be considered as a rare differential diagnosis of frontal headache, especially in patients who develop aortic regurgitation or chest pain for the first time.

Comment: Intrathoracic structural disease can rarely cause head and face pain. Disease of the mediastinal contents can cause throat pain or pain in the jaw. Relentless, deep, boring facial pain can rarely be the first manifestation of a lung tumor without metastases. Compression of the vagus nerve by the tumor or by mediastinal adenopathy presumably caused the facial pain. Pain in the teeth (molars) and ear can also be caused by malignant mediastinal tumors.

Cephalalgia 1998;18:583-584.

Obelieniene D, Bovim G, Schrader H, Surkiene D, Mickeviaiene D, Miseviaiene I, Sand T. Headache after whiplash: a historical cohort study outside the medico-legal context.

Headache is frequently reported as a chronic complaint after whiplash traumas. Criteria have been presented, but it has not been validated

whether any specific headache type emerges after a trauma with whiplash mechanism. In a questionnaire-based historical cohort design, 202 adult Lithuanian individuals were interviewed 1-3 years after experiencing a rear-end car collision. The questionnaire was designed so that a diagnosis of migraine and tension- type headache in accordance with the International Headache Society criteria could be made. "Possible cervicogenic headache" was diagnosed according to Sjaastad et al's minimal criteria. The diagnostic panorama in those with traumas was compared with that of an age- and sex-matched control group. The introductory questions did not reveal differences in headache frequencies between the traumatized and control groups (p=0.60). The prevalence of migraine and tension-type headache (both episodic and chronic) was also similar. A higher frequency of possible cervicogenic headache was observed in the traumatized group (10 vs 5), but the difference was not statistically significant (p = 0.28). Sixteen patients in the accident group had headache, >15 days per month, 11 of the 16 had similar complaints before the trauma, while 5 had worsened headache as compared to (the recollected headache) before the trauma. None of the patients with possible cervicogenic headache reported increased headache after the accident. Accordingly, the present results obtained outside the medico-legal context do not confirm that a specific headache pattern emerges 1-3 years after a

rear-end car collision.

Comment: Migraine and tension-type headache were no more common in victims of whiplash 1-3 years later than age- and sex-matched controls. It would be interesting to know the prevalence and frequency of headaches severe enough to impair functioning or cause work absenteeism in the two groups. This study was performed in Lithuania ▒ where litigation and compensation are not a factor.

Cephalalgia 1998;18:559-564.

Oaklander AL, Romans K, Horasek S, Stocks A, Hauer P, Meyer RA. Unilateral postherpetic neuralgia is associated with bilateral sensory neuron damage.

Shingles can cause chronic neuropathic pain (postherpetic neuralgia) long after skin lesions heal. To investigate its causes, we quantitated immunolabeled sensory neurites in skin biopsies from 18 subjects with and 16 subjects without postherpetic neuralgia after unilateral shingles. Subjects rated the intensity of their pain. Punch skin biopsies were evaluated from the site of maximum pain or shingles involvement, the homologous contralateral location, and a site on the back, distant from shingles involvement. Sections were immunostained with anti-PGP9.5 antibody, a pan-axonal marker, and the density of epidermal and dermal neurites determined. The group with postherpetic neuralgia had a mean density of 339 +/- 97 neurites/mm2 in shingles-affected epidermis compared with a density of 1,661 +/- 262 neurites/mm2 for subjects without pain. Neurite loss was more severe in epidermis than dermis. Unexpectedly, the group with pain had also lost half of the neurites in contralateral epidermis. Contralateral damage occurred despite the lack of contralateral shingles eruptions or pain, correlated with the presence and severity of ongoing pain at the shingles site, and did not extend to the distant site. Thus, the pathophysiology of postherpetic neuralgia pain may involve a new bilateral mechanism.

Ann Neurol 1998;44:789-795.

Dichgans M, Mayer M, Uttner I, Bruning R, MullerHocker J, Rungger G, Ebke M, Klockgether T, Gasser T. The phenotypic spectrum of CADASIL: Clinical findings in 102 cases.

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is an increasingly recognized autosomal dominant disorder that leads to cerebrovascular manifestations in early

adulthood. This study delineates the phenotypic spectrum and the natural history of the disease in 102 affected individuals from 29 families with biopsy-proven CADASIL. Recurrent ischemic episodes (transient ischemic attack [TIA] or stroke) were the most frequent presentation found in 71% of the cases (mean age at onset, 46.1 years; range, 30-66 years; SD, 9.0 years). Forty-eight percent of the cases had developed cognitive deficits. Dementia (28%) was frequently accompanied by gait disturbance (90%), urinary incontinence (86%), and pseudobulbar palsy (52%). Thirty-nine patients (38%) had a history of migraine (mean age at onset, 26.0 years; SD, 8.2 years), which was classified as migraine with aura in 87% of the cases. Psychiatric disturbances were present in 30% of the cases, with adjustment disorder (24%) being the most frequent diagnosis. Ten patients (10%) had a history of epileptic seizures. To delineate the functional consequences of ischemic deficits, we studied the extent of disability in different age groups. The full spectrum of disability was seen in all groups older than age 45. Fifty-five percent of the patients older than age 60 were unable to walk without assistance. However, 14% in this age group exhibited no disability at all. Kaplan-Meier analysis disclosed median survival times of 64 years (males) and 69 years (females). An investigation of the 18 multiplex families revealed marked intrafamilial variations.

Comment: The phenotypic heterogeneity of a specific genotype like CADASIL makes one wonder about traditional definitions of "disease." Should a disease be defined by its pathology (or pathophysiology) or genotype or both? Operational definitions of "diagnoses" like the IHS criteria almost certainly include heterogeneous disorders within the same diagnostic category. But, of course, diagnoses are not diseases.

Ann Neurol 1998;44:731-739.

Rowbotham M, Harden N, Stacey B, Bernstein P, MagnusMiller L. Gabapentin for the treatment of postherpetic neuralgia: A randomized controlled trial.

Context: Postherpetic neuralgia (PHN) is a syndrome of often intractable neuropathic pain following herpes zoster (shingles) that eludes effective treatment in many patients.

Objective: To determine the efficacy and safety of the anticonvulsant drug gabapentin in reducing PHN pain.

Design: Multicenter, randomized, double-blind, placebo-controlled, parallel design, 8-week trial conducted from August 1996 through July 1997.

Setting: Sixteen US outpatient clinical centers.

Participants: A total of 229 subjects were randomized.

Intervention: A 4-week titration period to a maximum dosage of 3600 mg/d of gabapentin or matching placebo. Treatment was maintained for another 4 weeks at the maximum tolerated dose. Concomitant tricyclic antidepressants and/or narcotics were continued if therapy was stabilized prior to study entry and remained constant throughout the study.

Main Outcome Measures: The primary efficacy measure was change in the average daily pain score based on an 10-point Likert scale (0, no pain; 10, worst possible pain) from baseline week to the final week of therapy. Secondary measures included average daily sleep scores, Short-Form McGill Pain Questionnaire (SF-MPQ), Subject Global Impression of Change and investigator-rated Clinical Global Impression of Change, Short Form-36 (SF-36) Quality of Life Questionnaire, and Profile of Mood States (POMS). Safety measures included the frequency and severity of adverse events.

Results: One hundred thirteen patients received gabapentin, and 89 (78.8%) completed the study; 116 received placebo, and 95 (81.9%) completed the study. By intent-to-treat analysis, subjects receiving gabapentin had a statistically significant reduction in average daily pain score from 6.3 to 4.2 points compared with a change from 6.5 to 6.0 points in subjects

randomized to receive placebo (P<.001). Secondary measures of pain as well as changes in pain and sleep interference showed improvement with gabapentin (P<.001), Many measures within the SF-36 and POMS also significantly favored gabapentin (P less than or equal to.01). Somnolence, dizziness, ataxia, peripheral edema, and infection were all more frequent in the gabapentin group, but withdrawals were comparable in the 2 groups (15 [13.3%] in the gabapentin group vs 11 [9.5%] in the placebo group).

Conclusions: Gabapentin is effective in the treatment of pain and sleep interference associated with PHN. Mood and quality of life also improve with gabapentin therapy.

JAMA 1998;280:1837-1842.

Holst D, Mollmann M, Ebel C, Hausman R, Wendt M. In vitro investigation of cerebrospinal fluid leakage after dural puncture with various spinal needles.

Postspinal headache is one of the most common complications of spinal anesthesia and has repeatedly led to controversy concerning needle size and configuration. In an in vitro investigation, we measured cerebrospinal fluid (CSF) leakage with Sprotte, Whitacre, Quincke, and Atraucan needles under physiological conditions in human dura. The puncture characteristics were examined under an electron microscope. The pencil-point needles show 2-3 times less leakage of CSF compared with the cutting Quincke needles of corresponding size. Between the Sprotte and the Whitacre needles, there were no significant differences. The least loss of CSF occurred with the 26-gauge Atraucan needle. Under the electron microscope, a sharply delineated, persistent perforation channel was shown with the Quincke needles, which may explain the high CSF loss. With pencil-point needles, which push the tissue apart bluntly, a large opening on the inside is found, with some tearing of the dura. However, in contrast to the cutting needles, a persistent perforation channel is not manifested. The 26-gauge Atraucan needle, which both cuts and pushes apart conically, shows a relatively discrete opening on the inside, with slight tears in the dura and arachnoidea but without a visible perforation channel. The results of our study show that larger needles (26-gauge Atraucan) that are easier to handle can lead to good and, in some cases even better, puncture results if they have characteristics of both the cutting and the pencil-point needles.

Implications: We compared several brands of pencil-point and standard cutting spinal needles of varying sizes. All pencil-point needles had less cerebrospinal fluid leakage, the least loss occurring with 26-gauge Atraucan needles. Electron microscopic examination of the dura after puncture showed characteristic findings with each needle type. We conclude that the combined cutting and pencil-point characteristics seen in the Atraucan needle may have clinical advantages.

Anesth Analg 1998;87(6):1331-1335.

Flaatten H, Thorsen T, Askeland B, Finne M, Rosland J, Hansen T, Ronhovde K, Wisborg T. Puncture technique and postural postdural puncture headache. A randomised, double-blind study comparing transverse and parallel puncture.

Background: This clinical study was conducted in order to investigate the effect of two different orientations of the bevel during dual puncture on development of postural postdural puncture headache (PPDPH).

Methods: Two hundred and eighteen patients aged 18 to 50 years scheduled for minor non-obstetric surgery using spinal anaesthesia (SA) were included in this randomised, double-blind study. Dual puncture was performed using a 0.42 mm O.D. (27-g) Quincke spinal needle with the orientation of the bevel parallel or transverse relative to the longitudinal axis of the dural cylinder. All patients were blinded with regard to the puncture technique,

and so was the anaesthesiologist performing a telephone interview 5 to 7 days postoperatively. The occurrence and duration of headache, backache and other complaints were recorded. Headache was classified as PPDPH or non-PPDPH, and intensity of the headache was registered using a numerical rating scale (NRS) from 0 to 10.

Results: Two hundred and twelve patients with a mean age of 35.3 years completed the study, 106 in each group. The two groups were comparable with regard to mean age, sex, local anaesthetics used and surgical procedure performed. Headache occurred in 44 patients postoperatively. PPDPH was diagnosed in 4/106 patients (3.8%) in the parallel group and 24/106 (22.6%) in the transverse group (P<0.0002). Postoperative backache occurred in 31 and 20 patients (parallel compared to transverse) (NS).

Conclusions: Dual puncture with the bevel of the needle transverse to the longitudinal axis of the dural cylinder gave significantly more cases of PPDPH than puncture with the bevel paralleI to this axis even when using a 27-g Quincke needle. When using Quincke bevelled needles care must be taken to assure that the orientation of the bevel is parallel to the longitudinal axis of the dural sac.

Acta Anaesthesiol Scand 1998;42:1209-1214.

Ferrari R, Leonard MS. Whiplash and temporomandibular disorders: A critical review.

Some authors have hypothesized a relationship between rear- impact motor vehicle collisions and subsequent symptoms of neck pain and temporomandibular disorders, or TMD, despite no facial impact. This article examines the TMD aspect in terms of the physiological basis and cultural factors influencing the reporting of such symptoms.

J Amer Dent Assn 1998;129:1739-1745.

Schievink WI, Smith KA. Nonpositional headache caused by spontaneous intracranial hypotension.

Comment: This 69 y.o. man awoke with headache and a whirring noise in both ears. An MRI brain scan showed bilateral subdural hematomas. The headache had never been affected by position (no worse in upright versus recumbent position). There had been no history of craniocervical or somatic trauma. Cisternography showed a focal CSF leak at the left lumbosacral junction. It is likely that the intracranial hypotension was asymptomatic until it produced the subdural hematomas.

Neurology 1998;51: 1768-1769

JimenezJimenez FJ, GarciaAlbea E, Zurdo M, Martinez-Onsurbe P, deVillaespesa AR. Giant cell arteritis presenting as cluster headache.

Comment: This 74 y.o. male presented with month history of episodic left supraorbital pains with abrupt onset and offset and duration of 15 to 20 minutes. He averaged 3-4 attacks per day and some attacks were nocturnal. The pain was associated with ipsilateral ptosis, lacrimation, and rhinorrhea. He also had polymyalgia rheumatica, jaw claudication, and elevated ESR (83 mm/hr). There was no mention of alcohol precipitating attacks and there was no attempt to trigger an attack with nitroglycerin. Prednisone provided rapid resolution of all symptoms. Over the years, I have seen case reports of organic disorders mimicking cluster headache. Just like "first migraine," new onset of cluster headache has to be scruitinized more carefully than typical episodic cluster attacks with multiple cycles separated by remissions lasting months or longer. In this

patient the late onset, polymyalgia rheumatica, and jaw claudication were suggestive of another disorder. If the ESR had been normal (which it is at least 10% of the time) and polymyalgia rheumatica and jaw claudication had been absent, the clinical findings and a positive response to steroids would have been consistent with the diagnosis of cluster headache.

Neurology 1998;51:1767-1768.

Cluff RS, Rowbotham MC. Pain caused by herpes zoster infection.

Postherpetic neuralgia (PHN) is a neuropathic pain disorder that occurs most often in the elderly. This painful condition is uniquely suited for clinical research, resulting in an emerging understanding of the pathophysiology of the persistent pain. Until recently, only the tricyclic antidepressants proved effective for PHN. Controlled trials of a wide variety of therapeutic strategies are in progress or have been recently completed.

Neurol Clin 1998;16(4):813.

Heikkila H, Heikkila E, Eisemann M. Predictive factors for the outcome of a multidisciplinary pain rehabilitation program on sick-leave and life satisfaction in patients with whiplash trauma and other myofascial pain: a follow-up study.

Objective: To evaluate the effects of a multidisciplinary rehabilitation program on sick-leave, coping resources and life satisfaction in whiplash patients and other pain patients.

Subjects: Forty patients suffering from symptoms after whiplash trauma and 33 patients with musculoskeletal pain in the neck or back were recruited for this study. Ninety- seven consecutive patients admitted to the Department of Neurosurgery with cervical pain, cervical disc herniation, or symptomatic spondylosis served as a control group.

Results: Decreased coping resources and poorer life satisfaction were observed for whiplash subjects at the beginning of the rehabilitation program compared to the control group from the Department of Neurosurgery. After the rehabilitation period 49% of the patients had improved their coping resources totalling to 63% after 2 years. At that follow-up 46% of patients had increased their life satisfaction. Furthermore, the group with whiplash injury showed a significant increase in sick absenteeism whereas the group without whiplash trauma had decreased their sick leave. Eighty-eight per cent of the subjects could be correctly classified according to their vocational outcome by means of discriminant function. The elapse of time since working, low life satisfaction, lack of increase in coping resources during the rehabilitation program, ethnic origin of the patient and living in the countryside predicted poor vocational outcome.

Conclusion: Our results suggest variables from the social environment and coping resources as useful predictors for treatment outcome.

Comment: Although physical factors may cause early symptoms, the course and prognosis for chronic whiplash syndrome may be influenced more by non-physical factors.

Clin Rehabil 1998;12:487-496.

OROFACIAL PAIN

Prinz JF. Physical mechanisms involved in the genesis of temporomandibular joint sounds.

Several different mechanisms are potentially capable of generating sounds in the temporomandibular joint (TMJ). These include impact, sliding and stick-slip friction, fluid dynamic effects and the release of elastic strain energy. It is the aim of this paper to provide a framework with which to separate sounds resulting from the different underlying causes. Each mechanism is described and its relevance to TMJ sounds and clinical significance discussed. Since it is not possible to observe these mechanisms in vivo the arguments are based mainly on analogies which are used to make predictions of the characteristic acoustic signatures of the sounds produced by these different mechanisms. In particular the changes in the characteristics of the sounds as parameters such as mandibular speed and loading are stressed. It is suggested that single short duration sounds (clicks) are due to impact, multiple short duration sounds (creaks) to stick- slip friction and defects of form and long duration sounds (crepitus) to simple sliding friction. Several other mechanisms which have no obvious clinical significance but which are capable of producing similar sounds are also described and methods of distinguishing them from the sounds that do have clinical implications are discussed.

Comment: Epidemiologic studies of TMD have shown that approximately 75% of people have at least one sign of TMD, and about 33% have at least one symptom (e.g., pain, joint sounds, limited jaw range of motion). It is estimated, however, that only 5% need treatment.

J Oral Rehabil 1998;25:706-714.

Orsini MG, Kuboki T, Terada S, Matsuka Y, Yamashita A, Clark GT. Diagnostic value of 4 criteria to interpret temporomandibular joint normal disk position on magnetic resonance images.

Objective: This study was undertaken to evaluate different criteria to establish normal disk position on magnetic resonance images.

Study design: Magnetic resonance image findings of 137 consecutive patients with temporomandibular disorders and 23 asymptomatic volunteers were used in this study. Three calibrated observers interpreted the images individually. Four closed-mouth and 1 open-mouth criteria were tested for their ability to define normal and abnormal temporomandibular joint disk positions on magnetic resonance images.

Results: For the 46 joints in the asymptomatic volunteers, the criterion that yielded the highest percentage of normal disk position diagnoses was the disk's intermediate zone (93.5%). Clock face criteria produced the following declining percentages of normal disk position diagnoses: 10 o'clock, 82.6%; 11 o'clock, 63.0%; and 12 o'clock, 39.1%. Similar results were obtained for the patients with temporomandibular disorders. In both groups, as the number of normal disk position diagnoses declined, the percentage of joints with a diagnosis of disk displacement with reduction increased. Conversely, the percentage of joints with a diagnosis of disk displacement without reduction (in the group of patients with temporomandibular disorders) did not appear to be substantially affected by the 4 closed-mouth disk position criteria.

Conclusions. These results suggest that the intermediate zone criterion for disk displacement is the more stringent criterion and the one that would yield the lowest number of false positives when the disk position is being judged in the closed-mouth sagittal view.

Oral Surg Oral Med Oral Patho. 1998;86:489-497.

Korszun A, Papadopoulos E, Demitrack M, Engleberg C, Crofford L. The relationship between temporomandibular disorders and stress-associated syndromes.

Objectives: The purpose of this study was to determine the comorbidity of temporomandibular disorders and other stress-associated conditions in patients with chronic fatigue syndrome and fibromyalgia.

Study Design: OF 92 patients who fulfilled the criteria for chronic fatigue syndrome or fibromyalgia (or both), 39 (42%) reported a prior diagnosis of temporomandibular disorder. Further questionnaires were sent to the members of this group, and 30 patients responded.

Results: Of the original 92 patients, of whom 42% reported temporomandibular disorders, 46% had histories of irritable bowel syndrome, 42% of premenstrual syndrome, and 19% of interstitial cystitis. Of the patients with temporomandibular disorders, the great majority reported an onset of generalized symptoms before the onset of facial pain. Despite this, 75% had been treated exclusively for temporomandibular disorders, usually with bite splints.

Conclusions: Patients appearing for treatment with chronic facial pain show a high comorbidity with other stress-associated syndromes. The clinical overlap between these conditions may reflect a shared underlying pathophysiologic basis involving dysregulation of the hypothalamic-pituitary-adrenal stress hormone axis in predisposed individuals. A multidisciplinary clinical approach to temporomandibular disorders would improve diagnosis and treatment outcomes for this group of patients.

Comment: Patients who have been diagnosed as having TMJ (?criteria) are also frequently diagnosed as having fibromyalgia, chronic fatigue syndrome, irritable bowel syndrome, and interstitial cystitis. These diagnoses are also common in chronic headache patients. Disabling chronic fatigue syndrome and fibromyalgia symptoms, in my experience, predict a poor response to pharmacotherapy. Interstitial cystitis is less commonly reported by chronic headache patients but such patients seem even less likely to respond to pharmacotherapy.

Oral Surg Oral Med Oral Patho.1998;86:416-420.

Gibbs SJ, Simmons HC. A protocol for magnetic resonance imaging of the temporomandibular joints.

The complex concepts and procedures of magnetic resonance imaging (MRI) are unfamiliar to many dentists. Similarly, many radiologists lack understanding of the clinical requirements of the dentist for accurate assessment of TMJ abnormalities. Thus, TMJ imaging procedures may be inadequate or incomplete, may vary from facility to facility, and sometimes from patient to patient in a given facility. A protocol for TMJ imaging is presented which meets dental requirements and is rapidly performed in the MRI facility. The protocol may be copied and attached to the prescription to the imaging center. It may be modified or expanded to accommodate specific patient requirements or equipment performance.

Cranio J Craniomandib Pract 1998;16:236-241.

Prinz JF. Subjective assessment of temporomandibular joint sounds.

If it could be shown that the human ear was sufficiently sensitive to describe TMJ sounds, there would be no need to use sophisticated electronic equipment to analyse the sounds. To test this, the ability of normal listeners to distinguish the subtle changes in position, pitch, duration and latency present in TMJ sounds is measured using triangle tests to determine the just-noticeable differences. The results suggest that the

human ear is a rather poor instrument for describing subtle differences in the position, duration and latency of TMJ sounds, but is capable of detecting small differences in frequency. It is therefore doubtful that the human ear can distinguish the reciprocal click associated with disc displacement with reduction from clicks due to defects of form on the basis of their relative position in the envelope of movement.

J Oral Rehabil 1998;25:765-769.

McKay DC, Christensen LV. Whiplash injuries of the temporomandibular joint in motor vehicle accidents: speculations and facts.

Referring to the temporomandibular joint (TMJ) of the human mandibular locomotor system, it has been asserted that displacement of the TMJ disc and inflammation of TMJ tissues are the results of acute and indirect trauma to the TMJ; on occasion this is allegedly experienced in motor vehicle accidents and commonly known as a TMJ whiplash injury. It is postulated that the TMJ whiplash injury is released in the occupant or occupants of a target vehicle when its rear end is impacted by the front end of a bullet vehicle. On the basis of detailed analyses of TMJ trauma/pain histories and TMJ magnetic resonance images, presented as circumstantial evidence in favour of the postulated TMJ whiplash injury, and detailed analyses of the mathematical biophysics of the mandibular locomotor system as well as direct experimental evidence, it is concluded that the postulated TMJ whiplash injury does not exist as a single and independent disease entity caused by motor vehicle accidents. If TMJ disc displacement and inflammation are present, they are expressions of an insidious and progressive pre-existing (pre-accident) disease entity that is comprised of TMJ synovitis/osteoarthritis (phase of inflammation with presence of immune system cells), TMJ internal derangement (phase of disc displacement and deformation with presence of proteinases), and TMJ osteoarthrosis (phase of degeneration with absence of immune system cells). For the asserted TMJ whiplash manoeuvre and ensuing injury to occur as postulated, the laws of physics and biology would have to be suspended.

J Oral Rehabil 1998;25:731-746.

Bergman H, Andersson F, Isberg A. Incidence of temporomandibular joint changes after whiplash trauma: A prospective study using MR imaging.

Objective: The purpose of this study was to describe the incidence of temporomandibular joint (TMJ) changes after a well-defined whiplash trauma.

Subjects and Methods: Sixty consecutively admitted patients with symptoms in the neck after rear-end traffic collisions underwent MR imaging of the TMJs within 3-14 days after the collisions. Fifty-three healthy volunteers constituted a control group.

Results: No statistically significant differences were found between the 60 patients and the 53 volunteers regarding frequency, stage, grade, or direction of TMJ disk displacement or joint effusion. MR imaging revealed that 45% of the control group and 53% of the patient group had a displaced disk in one or both TMJs ($p = .393$). Disk displacement was seen in 35% of TMJs in the control group and 40% of TMJs in the patient group. Effusion was seen in 8% of TMJs in the control group and 6% of TMJs in the patient group. No signs of bleeding or edema in the soft tissues were observed. In 15% of the patients, mild clinical symptoms in the TMJ or masticatory muscles developed in association with the trauma; in one third of these patients the symptoms were transient.

Conclusion: This prospective study does not show any significantly increased incidence of disk displacement, joint effusion, or any other injury to the TMJ after whiplash trauma that could be revealed by MR imaging.

Comment: TMJ dysfunction does not appear to be more frequent or severe in whiplash patients than control patients.

Am J Roentgenol 1998; 171:1237-1243.

DeLaat A, Svensson P, Macaluso GM. Are jaw and facial reflexes modulated during clinical or experimental orofacial pain?

A variety of jaw and facial reflexes can be evoked by orofacial mechanical or electrical stimuli. Because of its possible diagnostic utility in the management of pain and dysfunction of the masticatory system, the exteroceptive suppression that can be evoked in the masseter and temporalis muscles has been particularly investigated. A review of the different studies emphasizes the crucial importance of the area stimulated and the type of stimulation used to evoke the reflex. More recent studies have applied the necessary standardization of stimulus intensity, clenching levels, recording procedures, and unbiased interpretation of the reflex components in muscle electromyographic (EMG) activity. Controversial results have been reported regarding the differences in these inhibitory (and excitatory) reflex responses between temporomandibular disorder or headache patients and controls. Even if the absence of a second inhibitory phase in the masseteric EMG activity of the patients is a frequent finding, its sensitivity and specificity as a diagnostic tool for myogenous pain or bruxism remain to be tested. Controlled studies on the duration of the second exteroceptive suppression period in tension-type headache patients could not confirm the initially reported difference between patients and asymptomatic subjects. Studies that involve experimentally induced muscle pain could provide better insight into the characteristics of the afferent fibers and synaptic circuitry that are involved in the jaw and facial reflexes.

J Orofac Pain 1998;12:260-271.

Sonnesen L, Bakke M, Solow B. Malocclusion traits and symptoms and signs of temporomandibular disorders in children with severe malocclusion.

The present study reports the prevalence of the various traits of malocclusion, as well as the occurrence of associations between malocclusion, and symptoms and signs of temporomandibular disorders (TMD) in children selected for orthodontic treatment by the new Danish procedure for screening the child population for severe malocclusions entailing health risks. The sample comprised 104 children (56 F, 48 M) aged 7-13. Malocclusion traits were recorded at the time of selection, symptoms and signs of TMD were recorded at recall. The most prevalent malocclusion traits were distal molar occlusion (Angle Class II; 72 per cent), crowding (57 per cent), extreme maxillary overjet (37 per cent) and deep bite (31 per cent). Agenesis or peg-shaped lateral teeth were observed in 14 per cent of the children. The most prevalent symptom of TMD was weekly headache (27 per cent); the most prevalent signs of TMD were tenderness in the anterior temporal, occipital, trapezius, and superficial and profound masseter muscles (39-34 per cent). Seven per cent of the children were referred for TMD treatment. The Danish TMD screening procedure was positive in 26 per cent, while 20 per cent had severe symptoms (Aill), and 30 per cent had moderate signs (Dill) according to Helkimo (1974). Symptoms and signs of TMD were significantly associated with distal molar occlusion, extreme maxillary overjet, open bite, unilateral crossbite, midline displacement, and errors of tooth formation. The analysis suggests that there is a higher risk of children with severe malocclusions developing TMD. Errors of tooth formation in the form of agenesis or peg-shaped lateral teeth showed the largest number of associations with symptoms and signs of TMD; these associations have not previously been reported in the literature.

Eur J Orthodont 1998;20:543-559.

Woda A, Navez ML, Picard P, Gremeau C, PichardLeandri E. A possible therapeutic solution for stomatodynia (Burning mouth syndrome).

Stomatodynia is a difficult disease for both patients and clinicians. When facing true stomatodynia, ie, idiopathic burning mouth, patients are offered poorly effective treatment. This open study reports the results of local application of clonazepam (0.5 or 1 mg) two or three times daily in 25 subjects who suffered from idiopathic stomatodynia. At the first evaluation, 4 weeks after the beginning of treatment, a visual analogue scale (VAS) that represented the intensity of pain decreased significantly from 6.2 +/- 0.3 to 3.0 +/- 0.5. At the second evaluation, 3 to 29 months after the first consultation, the VAS scores dropped significantly further to 2.6 +/- 0.5. Analysis of the individual results showed that 10 patients were totally cured and needed no further treatment, 6 patients had no benefit at all, and the remaining 9 patients had some improvement but were not considered to be cured since they did not wish to stop the treatment. Blood level tests that were performed 1 and 3 hours after the topical application revealed the presence of small amounts of the drug (3.3 ng/mL +/- 0.66 and 3.3 ng/mL +/- 0.52, respectively). The hypothesis that clonazepam acts locally to disrupt the neuropathologic mechanism that underlies stomatodynia is proposed. The risk factors that are recognized for this condition could decrease the density and/or ligand affinity of peripheral benzodiazepine receptors. This, in turn, could cause spontaneous pain from the tissues concerned.

J Orofac Pain 1998;12:272-278.

Grushka M, Epstein J, Mott A. An open-label, dose escalation pilot study of the effect of clonazepam in burning mouth syndrome.

Objective. Current treatment for burning mouth syndrome is usually directed at correction of detected organic causes or is empiric, and it often involves the use of tricyclic antidepressants. Recently, there has been renewed interest in the use of benzodiazepines for burning mouth syndrome. The present study was designed to assess the effect of clonazepam in burning mouth syndrome.

Study design. Thirty patients, each with a chief complaint of mouth burning without oral mucosal lesions, were entered into the study. All patients underwent routine blood screens. Identified abnormalities were corrected, when possible, before clonazepam was prescribed. The starting dose was 0.25 mg daily, with an increase in dose of 0.25 mg on a weekly basis if symptoms continued.

Results. The subject population consisted of 29 women and 1 man. All subjects had been symptomatic (average premorbid burning intensity, 7.0 +/- 1.9 on 10-point scale) for 1 month to 12 years (mean, 3.9 +/- 3.4 years; median, 2.75 years), and 16% had had burning for more than 2 years. Three groups of patients were identified: those who experienced partial to complete relief with clonazepam and who were using the medication at the last follow-up (group 1; 43%); those who found the clonazepam helpful but withdrew from the medication because of side effects- usually drowsiness (group 2; 27%); and those who did not benefit from clonazepam (group 3; 30%). Among the 3 groups, age was found to be significantly lower for group 1 than for group 2 but not significantly lower for group 1 than for group 3. Although the difference did not reach significance, the mean dose of clonazepam appeared lower for group 1 patients than for the other 2 patient groups. The number of patients with burning for less than 2 years was larger in group 1 than in the other groups.

Conclusions. The results suggest that clonazepam may be helpful in burning mouth syndrome, inasmuch as 70% of patients (groups 1 and 2) experienced pain reduction with effects at low doses. These findings suggest that the mechanism of action of clonazepam may be specific and separate from the anxiolytic effect of the benzodiazepines and that clonazepam may represent

a useful therapy in a subset of patients with burning mouth syndrome. Double-blind, placebo-controlled trials are warranted.

Oral Surg Oral Med Oral Patho 1998;86:557-561.

Pertes RA. Differential diagnosis of orofacial pain.

Orofacial pain, especially if the problem is chronic, presents a diagnostic and management challenge to all health practitioners. This paper suggests how clinicians might simplify the diagnosis of orofacial pain. First, the pain is classified into one of the three basic pain categories: somatic, neuropathic, or psychogenic pain. Somatic pain results from noxious stimulation of normal neural structures. Neuropathic pain is caused by a structural abnormality in the nervous system. Psychogenic pain arises from psychic causes; there is no apparent physiologic or organic basis for the pain. The next step is to determine the tissue system from which the pain arises: intracranial, extracranial, musculoskeletal, neurogenous, or psychological. Finally, some of the more common orofacial pain syndromes within each category are discussed.

Mt Sinai J Med 1998;65:348-354.

Awad MA, Feine JS. Measuring patient satisfaction with mandibular prostheses.

Objectives: Previous research has shown that patients' evaluations of their prostheses correlate poorly with the clinicians' assessments, as well as with intraoral anatomic factors. It has been recommended that researchers conduct more studies that use patient satisfaction as the primary outcome measure in treatment evaluation and that more attention be paid to understanding exactly what measures of patient satisfaction represent. In this study, the relationship between patients' ratings of general satisfaction and their perceptions of different aspects of mandibular prostheses is investigated.

Methods: One hundred and twenty subjects applied to participate in a randomized controlled clinical trial comparing two types of mandibular prostheses: conventional dentures and implant prostheses. At baseline, they were asked to rate on 100 mm visual analog scales (VAS) factors that edentulous patients indicated were important to them. These included comfort,

ability to chew, stability, esthetics, ability to speak and ease of cleaning of their conventional dentures. Subjects were also asked to rate their general satisfaction with their dentures. In addition, they selected the one quality of their denture that they considered to be most important.

Results: Multiple regression methods revealed that gender, as well as patients' ratings of comfort, stability, esthetics, ability to chew and ability to speak with their prostheses contributed significantly to general satisfaction ($F<0.0001$). Furthermore, 89% of the variation in ratings of general satisfaction was explained by these factors. In addition, patients who considered ability to chew as the most important factor associated with their dentures rated their general satisfaction significantly higher than the other subjects ($P=0.0003$).

Conclusion: Patient satisfaction with conventional dental prostheses is highly dependent on gender, and the appearance and functionality of the appliance. The combined effect of these factors explained most of the variation in the satisfaction ratings.

Comment: This study is reminiscent of the fine study done by Russell Packard many years ago. What patients want and what we think they want are often not the same. Successful clinicians know how to satisfy their patients without enabling maladaptive behaviors. In a study of headache

clinic patients, patient satisfaction with the initial consultation predicts therapeutic success better than any specific therapeutic intervention for headache. (Fitzpatrick 1981)

Community Dent. Oral Epidemiol 1998;26:400-405.

OTHER TOPICS OF INTEREST

Knudsen JF, Friedman B, Chen M, Goldwasser JE. Ischemic colitis and sumatriptan use.

Sumatriptan succinate, a serotonin-1 (5-hydroxytryptamine-1) receptor agonist, is an antimigraine drug that is reported to act by selectively constricting intracranial arteries. Recently, vasopressor responses that are distinct from the cranial circulation have been demonstrated to occur in the systemic, pulmonary, and coronary circulations. Cases have been published of coronary vasospasm, myocardial ischemia, and myocardial infarction occurring after sumatriptan use. We report on the development of 8 serious cases of ischemic colitis in patients with migraine treated with sumatriptan.

Arch Intern Med 1998;158:1946-1948.

Murphy DL, Andrews AM, Wichems CH, Li Q, Tohda M, Greenberg B. Brain serotonin neurotransmission: An overview and update with an emphasis on serotonin subsystem heterogeneity, multiple receptors, interactions with other neurotransmitter systems, and consequent implications for understanding the actions of serotonergic drugs.

Knowledge about serotonergic neurotransmission has been expanding rapidly. Recent research has delineated 15 molecularly different serotonin receptors and multiple, discrete neuronal and nonneuronal (including endocrine) pathways and mechanisms that mediate the many functions of serotonin. Nonetheless, gaps remain regarding aspects of the anatomy and physiology of serotonin in its roles as a neurotransmitter, a neuromodulator, and a hormone. Few serotonin receptor-selective drugs are available for clinical use. A group of selective serotonin reuptake inhibitors (SSRIs) remain the agents with greatest therapeutic utility, although the mechanisms underlying their delayed efficacy, which clearly result from adaptive consequences following repeated administration rather than early uptake inhibition of serotonin by itself, are incompletely understood and appear to involve changes in signal transduction and gene expression in serotonergic and other neurotransmitter systems.

J Clin Psychiat 1998;59:4-12.

Hsiang JNK, Poon WS, Yu ALM. Postconcussion syndrome following mild head injury: how significant when it is work-related?

Postconcussional complaints are common after mild head injury. These symptoms can be so severe that some patients are unable to return to their previous employment. The purpose of this study is to investigate how important is work-related injury as a factor in determining the degree of disability caused by postconcussional symptoms. We studied 67 patients suffering from postconcussion syndrome after a mild head injury. These patients were divided into two groups, work-related injury and non-work-related injury. The results of this study demonstrated that the median duration of sick leave and the median amount of compensation were

significantly higher in the work-related group (8 months vs. 1 month, P = 0.0007; US$9000 vs. US$500, P = 0.0035, respectively). Only 41% of the work-related injured patients returned to work, compared with 85.7% in the nonwork-related injury group (P = 0.0022). The results of this study strongly suggested that work-related injury is a significant factor in determining the degree of disability associated with postconcussion syndrome.

J Clin Neurosci 1998;5:399-401.

Charney DS. Monoamine dysfunction and the pathophysiology and treatment of depression.

Alterations in noradrenergic and serotonergic function in the central nervous system (CNS) have been implicated in the pathophysiology of depression and the mechanism of action of antidepressant drugs. Based on changes in norepinephrine and serotonin metabolism in the CNS, it has been postulated that subgroups of patients with differential responses to norepinephrine and serotonin reuptake inhibitors may exist. Alpha-Methylparatyrosine (AMPT), which causes rapid depletion of brain catecholamines, has been used as a noradrenergic probe to test the hypothesis that changes in neurotransmission through the catecholamine system may underlie the therapeutic response to norepinephrine reuptake inhibitors. Brain serotonin is dependent on plasma levels of the essential amino acid tryptophan. Rapid tryptophan depletion, in the form of a tryptophan-free amino acid drink, has been used as a serotonergic probe to identify therapeutically responsive subsets of patients. Using these probes, we have recently examined the behavioral effects of reduced concentrations of brain monoamines on depressed patients treated with a variety of serotonin selective reuptake inhibitors (SSRIs) or the relatively norepinephrine-selective antidepressant desipramine, during 3 different states: drug-free and depressed; in remission on antidepressant drugs; and drug-free in remission. The results of a series of investigations confirm the importance of monoamines in the mediation of depressed mood, but also suggest that other brain neural systems may have more of a primary role than previously thought in the pathophysiology of depression. Noradrenergic and serotonergic probes may be used in time to identify subsets of depressed patients to determine which patients might respond differentially to the new selective norepinephrine reuptake inhibitors or SSRIs.

Comment: Whether major depression can be divided into "noradrenergic" and "serotonergc" categories is questionable. No drug has been found to be more effective than the heterocyclic agents in the treatment of major depression. Most claims for differential efficacy are limited to alternative classifications of depression, such as "atypical depressions," which may respond better to monoamine oxidase inhibitors. Selecting antidepressant medication on the basis of target symptoms may provide greater relief of some symptoms during the first few weeks of therapy. Sedating antidepressants may be more useful for agitated depression or insomnia in the first weeks of therapy but such neurovegetative symptoms will usually improve with "activating" antidepressants with fewer long-term side effects. Safety and compliance are probably more important considerations for treatment of major depression. Amitriptyline in doses necessary to relieve depression may have dose-limiting side effects. When headache patients have comorbid depression, psychiatric consultation should be obtained. The most effective and safest antidepressant should be used whether or not the agent has been shown effective in the treatment of migraine or tension-type headache.

J. Clin Psychiat 1998;59:11-14.

Zink T, Chaffin J. Herbal `health' products: What family physicians need to know.

Patients who self-medicate with herbs for preventive and therapeutic purposes may assume that these products are safe because they are "natural," but some products cause adverse effects or have the potential to interact with prescription medications. The United States lacks a regulatory system for herbal products. Although only limited research on herbs has been published, St John's wort shows promise as a treatment for depression. Ginkgo biloba extract is possibly effective for cerebrovascular insufficiency and dementia. Feverfew is used extensively in Canada for migraine prophylaxis but needs more rigorous study. Ephedrine has been regulated by many states because its misuse has been associated with several deaths. Echinacea is being tried as an agent for immune stimulation, and garlic is under study for cholesterol-lowering properties, but both require more study. Physicians should educate themselves and their patients about the efficacy and adverse interactions of herbal agents and the limitations of our present knowledge of them.

Comment: Many patients genuinely believe that "natural" means harmless or safe. Remind patients that tobacco, black nightshade, castor beans, and hemlock are also natural. Of course, overuse and inappropriate use of prescription medications causes far more deaths (e.g., over 7500 deaths each year from nonsteroidals) than herbal potions. For headache patients requesting a "natural" remedy, riboflavin and fever few are reasonable options.

Amer Fam Physician 1998;58:1133-1140.

Sullivan MJL, Stanish W, Waite H, Sullivan M, Tripp DA. Catastrophizing, pain, and disability in patients with soft-tissue injuries.

The present study examined the role of catastrophizing in predicting levels of pain and disability in a sample of individuals who had sustained soft-tissue injuries to the neck, shoulders or back following work or motor vehicle accidents. Participants were 86 (27 men, 59 women) consecutive referrals to the Atlantic Pain Clinic, a multidisciplinary treatment centre for the management of persistent pain disorders. Findings revealed that catastrophizing, measured by the Pain Catastrophizing Scale (PCS; Sullivan, M.J.L. Et al., Psychol. Assess., 7 (1995) 524-532) was significantly correlated with patients' reported pain intensity, perceived disability and employment status. The results of a regression analysis further showed that catastrophizing contributed to the prediction of disability over and above the variance accounted for by pain intensity. In addition, catastrophizing was associated with disability independent of the levels of depression and anxiety. The rumination subscale of the PCS was the strongest predictor of pain and disability. Theoretical and clinical implications of the findings are discussed.

Comment: If positive expectations can relieve pain, it makes sense that negative expectations can intensify pain and disability.

Pain 1998;77:253-260.

Brooks H, Elton CD, Smart D, Rowbotham DJ, McKnight AT, Lambert DG. Identification of nociceptin in human cerebrospinal fluid: comparison of levels in pain and non-pain states.

We have measured plasma and cerebrospinal fluid (CSF) concentrations of nociceptin, the endogenous agonist of the orphan opioid receptor like receptor (ORL-1). We studied two groups of ten patients presenting for elective Caesarean section (Group E) or in established labour and requiring combined spinal epidural anaesthesia for pain relief (Group L). Nociceptin was identified in all CSF samples with mean +/- SD concentrations of 52.49 +/- 34.25 and 63.39 +/- 33.26 pg/ml in groups E and L, respectively. Nociceptin was identified in 16/20 plasma samples with mean +/- SD concentrations of 7.59 +/- 21.58 and 13 73 +/- 23.79 pg/ml in groups E and L, respectively. CSF concentrations were significantly higher than plasma

concentrations and there were no differences between groups E and L. These data report the first measurements of CSF nociceptin in man and show no association with the acute pain of labour.

Comment: In the course of cloning the μ, k, and d opiate receptors, an orphan receptor, ORL1 (for opioid-like receptor 1), that did not bind any of the opioids with high affinity was identified. The natural ligand of this receptor has now been identified. It is a 17-amino-acid polypeptide that resembles dynorphin-17. However, upon intracerebral injection in experimental animals, it causes hyperalgesia rather than analgesia. On that basis, it has been named nociceptin. Nociceptin and its receptor are present in many areas in the CNS, including the hypothalamus, brain stem, and dorsal horn, and it seems likely that they play a role in pain transmission.

Pain 1998;78:71-73.

Nebe J, Keidel M, Ludecke C, Diener HC. Pain quantification following whiplash injury by means of computer-aided pressure algesimetry.

In patients with an acute cervicocephalic pain syndrome following whiplash injury (n=12), pressure-pain scores for the splenius and the trapezius muscles on both sides, for the fingers on both sides and for the skull were recorded and compared to a control group. A computer-aided pain measurement was applied, which is presented as an improvement of pressure algesimetry. During constant application of pressure stimuli, the patient rated the increasing pain on a visual analogue scale, resulting in a curve of pain intensity against time. Slope and integral of the curve proved to be the most reliable parameters. After whiplash injury, significantly increased pain scores were found for the splenius muscle on both sides, for the left trapezius muscle and for the left finger whereas there was only a tendency of increased pain at the other stimulation sites. The presented method allows quantification of the cervical syndrome with neck and shoulder muscle sprain caused by whiplash injury. This objective and rater-independent method is of great value for diagnostic, therapeutic and medico-legal purposes in the assessment of the disease course and in clinical therapy trials.

Comment: Pain assessment can be quantifiable and reproducible but not necessarily "objective." The increased pain score for the left finger after whiplash is interesting.

Nervenarzt 1998;69:924-928.

Partonen T, Lonnqvist J. Seasonal affective disorder.

Seasonal affective disorder (SAD) is a form of recurrent depressive or bipolar disorder, with episodes that vary in severity. Seasonal patterns of depressive episodes are common, but SAD seems to be less common than such patterns suggest. SAD was at first believed to be related to abnormal melatonin metabolism, but later findings did not support this hypothesis. Studies of brain serotonin function support the hypothesis of disturbed activity. The short-allele polymorphism for serotonin transporter is more common in patients with SAD than in healthy people. Atypical depressive symptoms commonly precede impaired functioning, and somatic symptoms are frequently the presenting complaint at visits to family physicians. The best treatment regimens include 2500 lx of artificial light exposure in the morning. When patients seem to have no response or to prefer another treatment, antidepressants should be considered.

Lancet 1998;352:1369-1374.

Barbone F, McMahon AD, Davey PG, Morris AD, Reid IC, McDevitt DG, MacDonald TM. Association of road-traffic accidents with benzodiazepine use.

Background: Psychomotor studies suggest that commonly prescribed psychoactive drugs impair driving skills. We have examined the association between the use of psychoactive drugs and road-traffic accidents.

Methods: We used dispensed prescribing as a measure of exposure in a within-person case-crossover study of drivers aged 18 years and over, resident in Tayside, UK, who experienced a first road-traffic accident between Aug 1, 1992, and June 30, 1995, and had used a psychoactive drug (tricyclic antidepressant, benzodiazepine, selective serotonin-reuptake inhibitor, or other psychoactive drug [mainly major tranquillisers]) between Aug 1, 1992, and the date of the accident. For each driver, the risks of having a road-traffic accident while exposed and not exposed to a drug were compared.

Findings: 19386 drivers were involved in a first road-traffic accident during the study period. 1731 were users of any study drug. On the day of the accident, 189 individuals were taking tricyclic antidepressants (within patient exposure odds ratio for an accident 0.93 [95% CI 0.72-1.21]), 84 selective serotonin-reuptake inhibitors (0.85 [0.55-1.33]), 235 benzodiazepines (1.62 [1.24-2.12]), and 47 other psychoactive drugs (0.88 [0.62- 1.25]). The risk associated with benzodiazepine use decreased with increasing driver's age and was greater when the breath test for alcohol was positive.The increased risk with benzodiazepines was significant for long-half-life drugs, used as anxiolytics, and for short- half-life hypnotics (all zopiclone).

Interpretation: Users of anxiolytic benzodiazepines and zopiclone were at increased risk of experiencing a road-traffic accident. Users of anxiolytic benzodiazepines and zopiclone should be advised not to drive.

Comment: Interpretation of these results seems reasonable. Nine percent (9%) of individuals involved in a first-time road accident were taking psychoactive drugs. A dose-response relation was evident with benzodiazepines. The accident was judged to the driver's fault in 70% of accidents when the driver used benzodiazepines. The risk associated with benzodiazepine use was highest among drivers younger than 30 years; it decreased with increasing age and was not raised in people aged 65 and over. There were no significant differences between men and women. In the discussion, the authors point out that one can not say that the association was definitely related to the medication or the disorder for which the medication was prescribed. The authors used a dispensing database that would have allowed them to compare drug use of patients with the drug use of the general population. Unfortunately, these results were not provided. It would be interesting to know what percentage of drivers not involved in an accident in the same time period were taking psychoactive medication. If 10% of the general population is taking psychoactive medication and 10% of drivers not involved in an accident are taking psychoactive medication, then one would have to question the authors' interpretation and recommendations.

Lancet 1998;352:1331-1336.

Dalal S, Melzack R. Potentiation of opioid analgesia by psychostimulant drugs: A review.

Recent research has investigated drug combinations that enhance the analgesic effectiveness of their component substances. Many studies have examined the combination of opioids and psychostimulant drugs, such as amphetamine and methylphenidate. Despite the positive results reported in the literature, this combination is rarely used in clinical practice. The purpose of this paper is to review the literature on the opioid-amphetamine combination. Experiments with animal and human subjects provide convincing evidence that d-amphetamine or methylphenidate potentiate the analgesic effects of morphine Psychostimulant drugs have been shown in animal studies

to possess intrinsic analgesic properties and to have the ability to enhance the analgesic properties of opioids when both types of drugs are given in combination. Studies with human subjects have confirmed the enhancement of opioid analgesia by amphetamines and, in addition, have demonstrated that psychostimulant drugs produce a decrease in somnolence and an increase in general cognitive abilities. The greater cognitive alertness, moreover, allows the use of larger opioid doses, which can produce a substantial increase in analgesia. These results indicate another possible method to enhance the quality of life in patients with difficult pain problems. Although the enhanced cognitive effects are well established the effects on pain need further study to determine the mechanisms of action and the drug combinations and administration patterns that would maximize their effects.

J Pain Symptom Manage 1998;16:245-253.

Dalal S, Melzack R. Psychostimulant drugs potentiate morphine analgesia in the formalin test.

Recent research has shown that the psychostimulant drug dextroamphetamine can increase the analgesia produced by opioids. Despite the strong, positive results in human clinical subjects and in animals, this combination is rarely used in clinical practice. The purpose of this paper is to investigate whether the psychostimulant drug methylphenidate (MP) can potentiate morphine analgesia in the rat formalin test, and to compare its effectiveness to that of dextroamphetamine (AMP). The formalin test was used because its long-lasting pain of moderate intensity resembles human clinical pain. Two different drug administration times were used to observe whether the early phase of the formalin response would be differentially affected by the drugs. At Drug Administration Time 1, rats received morphine 30 min prior to the formalin injection (-30 min) and MP or AMP 20 min prior to the formalin injection (-20 min). At Drug Administration Time 2, rats received morphine 10 min prior to the formalin injection (-10 min) and MP or AMP immediately prior to the formalin injection (0 min). All drugs were given subcutaneously. The results indicate that low doses of MP or AMP potentiate the analgesic effects of morphine. The clinical value of these drug combinations merits further investigation in animals and in humans.

J Pain Symptom Manage 1998;16:230-239.

Dellemijn PLI, vanDuijn H, Vanneste JAL. Prolonged treatment with transdermal fentanyl in neuropathic pain.

Forty-eight patients with noncancer neuropathic pain who had participated in a randomized controlled trial with intravenous fentanyl (FENiv) infusions received prolonged transdermal fentanyl (FENtd) in an open prospective study. Pain relief, side effects, tolerance, psychological dependence, mood changes, and quality of life were evaluated. The value of clinical baseline characteristics and the response to FENiv also was evaluated in terms of the outcome with long-term FENtd. Eighteen patients stopped prematurely because of insufficient pain relief, side effects, or both. Among the remaining 30 patients completing the 12-week dose titration protocol, pain relief was substantial in 13 and moderate in five. Quality of life improved (23%, $P < 0.01$). Psychological dependence or the induction of depression was not observed. In only one patient did tolerance emerge. There was a significant positive correlation between the pain relief obtained with FENiv and that with prolonged FENtd ($r = 0.59$, $P < 0.0001$). We conclude that (1) long-term transdermal fentanyl may be effective in noncancer neuropathic pain without clinically significant management problems and (2) A FENiv-test may assist in selecting neuropathic pain patients who might benefit from prolonged treatment with FENtd.

Comment: It was once thought that opiates were ineffective for neuropathic pain. This was probably due to inadequate dosing.

J Pain Symptom Manage 1998;16:220-229.

Settle EC. Antidepressant drugs: Disturbing and potentially dangerous adverse effects.

Adverse effects associated with antidepressant drug therapy rarely cause significant morbidity or mortality. Nevertheless, the successful management of patients with depression requires recognition of potential adverse effects that have serious consequences, which include the discontinuation of otherwise effective therapy. The aim of this overview is to highlight the more common and potentially deleterious adverse effects of both older and newer classes of antidepressant drugs. Major adverse effects attributed to the tricyclic antidepressant drugs (TCAs) include conduction defects and lethal overdose. Most worrisome with the selective serotonin reuptake inhibitor drugs (SSRIs) is the serotonin syndrome. Although rare, this syndrome can be insidious and lethal. Recent trends toward the use of medication combinations and augmentation therapies significantly enhance the risk of serotonin syndrome. Cognitive impairment also may occur, especially with the TCAs. Apathy is occasionally a problem with SSRI therapy. The syndrome of inappropriate antidiuretic hormone (SIADH) has been reported with most antidepressant drugs but appears to be more common with serotonergic agents and in elderly patients. Although seizures are uncommon in patients receiving antidepressant therapy, the risk must be understood by both the patient and the clinician. Adverse effects related to sexual function are common, especially with TCAs, SSRIs, and venlafaxine. Sexual dysfunction often leads to noncompliance and self-discontinuation of therapy. Sleep disturbances are common in patients with depression, and recent data illustrate how crucial sleep regulation is to mood. Antidepressant drugs vary in their sleep effects. Although antidepressant drugs can cause a variety of adverse effects, these drugs save lives and their benefits far exceed their risks.

J Clin Psychiat 1998;59:25-30.

Riley JL, Robinson ME, Kvaal SA, Gremillion HA. Effects of physical and sexual abuse in facial pain: Direct or mediated?

Research has identified a relationship between a history of physical and/or sexual abuse and a range of psychological, functional, and physical factors; however, the nature of this relationship has not been tested, We hypothesize two different mechanisms through which an abuse history could influence later life distress and dysfunction. A history of abuse could increase an individual's vulnerability to emotional distress or could increase an individual's tendency to attend, amplify, and over-interpret somatic symptom. The purpose of this study was to test the influence of emotional distress and somatic focus on the relationship between a history of physical and/or sexual abuse and later chronic pain- related disability in patients with temporomandibular disorders. The subjects were 139 female patients evaluated at a facial pain clinic. Of the 139 subjects, 49% (n = 69) reported a history of physical and/or sexual abuse. Abused subjects reported significantly higher levels of anxiety, depression, and somatic symptoms than nonabused subjects. Path analysis with latent variables, using the LISREL-8 (Scientific Software International, Inc., Chicago, Illinois) statistical program was used to test the hypothesized relationships. When emotional distress and somatic focus were tested as mediators, the path coefficient from somatic focus to physical functioning was significant (beta = -0.38) while the path coefficient from negative emotion to physical functioning was not significant. These results favor somatization as the hypothesized mechanism over the emotional distress vulnerability hypotheses.

Comment: Physical and sexual abuse is identified in about one-third of patients with psychogenic pseudoseizures and a history of abuse is frequently elicited in patients with dissociative disorders. Patients with

chronic pelvic pain appear to have an increased likelihood of having been sexually molested, raped, or physically abused (Walker et al. 1988). Abuse appears to predict a poor response to standard medical therapy for chronic daily headache. Unfortunately, accurate statistics regarding the incidence and prevalaence of abuse are difficult to obtain. How many women with a history of abuse suffer from somatoform and dissociative disorders? Probably a small minority but no one knows for sure.

Cranio J Craniomandib Pract 1998;16:259-266.

Manford M, Andermann F. Complex visual hallucinations - Clinical and neurobiological insights.

Complex visual hallucinations may affect some normal individuals on going to sleep and are also seen in pathological states, often in association with a sleep disturbance. The content of these hallucinations is striking and relatively stereotyped, often involving animals and human figures in bright colours and dramatic settings. Conditions causing these hallucinations include narcolepsy-cataplexy syndrome, peduncular hallucinosis, treated idiopathic Parkinson's disease, Lewy body dementia without treatment, migraine coma, Charles Bonnet syndrome (visual hallucinations of the blind), schizophrenia, hallucinogen-induced states and epilepsy. We describe cases of hallucinosis due to several of these causes and expand on previous hypotheses to suggest three mechanisms underlying complex visual hallucinations. (i) Epileptic hallucinations are probably due to a direct irritative process acting on cortical centres integrating complex visual information. (ii) Visual pathway lesions cause defective visual input and may result in hallucinations from defective visual processing or an abnormal cortical release phenomenon. (iii) Brainstem lesions appear to affect ascending cholinergic and serotonergic pathways, and may also be implicated in Parkinson's disease. These brainstem abnormalities are often associated with disturbances of sleep. We discuss how these lesions, outside the primary visual system, may cause defective modulation of thalamocortical relationships leading to a release phenomenon. We suggest that perturbation of a distributed matrix may explain the production of similar, complex mental phenomena by relatively blunt insults at disparate sites.

Comment: Excellent review for neurologists asked to see migraine patients with visual hallucinations. Visual hallucinations can be of two types: 1) positive or irritative phenomena due to epilepsy or migraine; and 2) negative or release phenomena related to abnormal visual input or defective modulation of thalamocortical circuits by brainstem centers.

Brain 1998;121:1819-1840.

Vatine JA, Tsenter J, Nirel R. Experimental pressure pain in patients with complex regional pain syndrome, Type I (Reflex sympathetic dystrophy).

Research in animals shows that the levels of neuropathic pain expression is genetically associated with a characteristic response profile to sensory stimuli. The aim of the present investigation was to examine if pressure algometry can identify a specific pain sensitivity profile in patients with complex regional pain syndrome, Type I (reflex sympathetic dystrophy), and to distinguish complex regional pain syndromes from other chronic pain dysfunction syndromes. Pressure pain threshold and pain tolerance measured at the sternum in 17 patients with complex regional pain syndrome, Type I (reflex sympathetic dystrophy), were compared with values obtained in 13 patients suffering from other chronic pain dysfunction syndromes and in a control group of 24 pain-free volunteers. The pressure algometer consisted of a force displacement transducer with a 0.25 cm(2) tip connected to a recorder. The rate of force application was 1 kg/0.25 cm(2)/s. The difference between threshold and tolerance was defined as the pain sensitivity range. Young patients with complex regional pain syndrome (<40 yr) demonstrated a significantly higher mean pain sensitivity range

compared with young subjects who had chronic pain or who were pain-free. Mean threshold and tolerance values were significantly lower in patients with complex regional pain syndrome (2.7 +/- 1.0 kg (mean +/- standard deviation) and 5.4 +/- 2.0 kg, respectively) and in patients suffering from other chronic pain syndromes (2.6 +/- 1.1 and 4.6 +/- 1.7 kg) than in healthy subjects (5.4 +/- 2.3 and 8.4 +/- 2.6 kg). Women in the chronic pain group exhibited a significantly lower pressure pain threshold than all other subgroups. Regardless of group, women exhibited lower pressure pain tolerance than men. In conclusion, the study contained herein shows a specific pain sensitivity profile to experimental stimuli behavior in young patients with complex regional pain syndrome expressed by a large pressure pain sensitivity range, at a location away from the painful area. However, one single pressure pain measurement over the sternum is insufficient for differentiation of patients with complex regional pain syndrome from those with chronic pain because of intersubject variation.

Comment: Young patients with complex regional pain syndrome (reflex sympathetic dystrophy) were more sensitive to experimentally induced pain (sternum pressure) than other chronic pain patients or normal controls.

Amer J Phys Med. Rehabil 1998;77:382-387.

Binzer M, Eisemann M. Childhood experiences and personality traits in patients with motor conversion symptoms.

A total of 30 patients with newly diagnosed motor conversion disorder were consecutively investigated by means of a Swedish self-rating inventory designed to assess perceived parental rearing practices (EMBU), and the Karolinska Scale of Personality (KSP). DSM Axis I and II psychopathology was assessed using a Structured Clinical Interview (SCID), and comparisons were made with 30 age- and sex-matched in-patients with motor symptoms due to a neurological disorder. Depression, the presence of a personality disorder and also poor schooling proved to be significantly associated with motor conversion disorder. The index patients perceived a high degree of parental rejection as well as low levels of affection and emotional warmth during childhood, but contrary to most previous studies, childhood physical and/or sexual abuse was not found to be associated with motor conversion disorder.

Comment: Childhood physical and/or sexual abuse were not found to be associated with motor conversion disorder. Conversion syndromes in children may occur without evidence of serious psychopathology and generally have a better prognosis than adult patients with conversion disorder.

Acta Psychiatr Scand 1998;98:288-295.

Wheatley D. Sex, stress and sleep.

One of the main sequelae to prolonged stressful situations is the development of depressive illness, which is usually accompanied by sexual dysfunction, insomnia and anxiety. The SSRIs that are used to treat depression may themselves aggravate these symptoms further and so delay recovery from the `stress-illness vicious circle'. These problems would appear to be considerably less with the newer sedative antidepressant drugs, such as nefazodone and mirtazapine. In a small (N = 14) open-label study, data on these factors was recorded before and after 5-weeks treatment with mirtazapine. There were highly significant improvements on the Hamilton Depression and Anxiety rating scales and also on the Sexual Stress and Sleep Problems items of the Wheatley Stress Profile (WSP) (p = 0.0001 respectively).

Comment: Initiating an SSRI at low dose with gradual increments over a period of several weeks can minimize stimulant side effects. When depression and anxiety symptoms are more severe, however, one may have to use a hypnotic or anxiolytic agent in the early phase of SSRI therapy.

Zoldipem can reduce insomnia without affecting the sleep architecture. Zoldipem has minimal risk of physical and psychic dependency. Zolpidem is a non-benzodiazepine hypnotic that attaches to the benzodiazepine omega-1 receptor. The newer sedative antidepressant drugs such as nefazodone and mirtazapine can treat depression without unwanted stimulant side effects (anxiety and insomnia).

Stress Medicine 1998; 14:245-248.

Xiao R, Beck O, Hjemdahl P. On the accurate measurement of serotonin in whole blood.

Background: Levels of serotonin (5-hydroxytryptamine; 5-HT) in whole blood reflect the levels in the platelets, but there are problems with instability of 5-HT in measurement of whole blood extracts. We therefore developed and validated an assay for whole blood 5-HT using HPLC with fluorometric detection. The procedure involved collecting blood in EDTA vacutainer tubes and aliquoting it with internal standard, alpha-methyl-5-HT, before freezing. The aliquots were thawed on ice and proteins precipitated with perchloric acid containing EDTA and ascorbic acid. The 5-HT was stable in fresh whole blood for 24 h after sampling when stored at room temperature, refrigerated, or ice-cooled. Measurements of the levels of 5-HT in blood collected in heparin, citrate or EDTA were similar, but in blood collected in ACD-buffer the levels were similar to 25% lower. Cell lysis by sonication decreased the 5-HT levels, but this was compensated for by the internal standard. Determinations of 5-HT by HPLC were in good agreement with those by gas chromatography - mass spectrometry. The intra-individual variability between days was 3.6% (n = 6). However, single and repeated ingestion of bananas, which are rich in 5-HT, elevated 5-HT in whole blood, indicating dietary influences on platelet 5-HT.

Comment: The platelet has been proposed as a model for the central serotonergic neuron. Given the widespread distribution of serotonin. receptors in the brain and multiple types and subtypes of receptors, are peripheral measurements of blood or platelet serotonin informative for pain and mood disorders?

Scand J Clin Lab Invest 1998; 58:505-510.

Clarke DM. Psychological factors in illness and recovery.

To review evidence that psychological factors affect the course of physical illness three areas are examined: epidemiological evidence showing the levels of psychiatric disturbance co-morbid with physical illness; health services research showing the burden of disease and care associated with this co-morbidity; randomised, controlled trials of psychological interventions in cancer, myocardial infarction and irritable bowel syndrome. There is substantial psychiatric co-morbidity with physical illness which is associated with increased disability, mortality and utilisation of health-care resources (primary care visits, hospitalization, length of hospital stay, cost). A small number of controlled intervention studies have shown the efficacy of psychological interventions to prolong survival in cancer and myocardial infarction, and to improve symptomatology in irritable bowel syndrome and other chronic somatizing conditions. Psychological factors do significantly affect outcomes of physical illness. The role of psychological treatments, alongside somatic therapies, needs further study.

N Z Med J 1998;111:410-412.

Brey RL, Escalante A. Neurological manifestations of antiphospholipid

antibody syndrome.

Thrombosis, thrombocytopenia, recurrent fetal loss and a variety of non-thrombotic neurological disorders have all been associated with antiphospholipid antibodies (aPL). Cerebral ischemia associated with aPL is the most common arterial thrombotic manifestation. Depression, cognitive dysfunction, depression and psychosis have all been associated with aPL. The presumed pathophysiologic mechanism underlying these manifestations is thought to be a result of cerebral ischemia in some, but not all cases. Seizures, chorea and transverse myelitis all appear to be associated with aPL. An interaction between aPL and central nervous system cellular elements rather than aPL- associated thrombosis seems to be a more plausible mechanism for these clinical manifestations. Migraine on the other hand, does not appear to be associated with aPL in either lupus or non-lupus populations. Neuroimaging studies show an increased frequency of brain abnormalities in patients with aPL, but none appear to be specific. The best treatment strategy for preventing neurological manifestations of aPL is not fully defined. For thrombotic manifestations, both antiplatelet and anticoagulant therapies have been suggested. In some patients, immunosuppressant therapy has been used. For non-thrombotic manifestations, some combination of immunosuppressant therapy and symptomatic treatment may be warranted.

Lupus 1998;7:S67-S74.

Jarvis B, Coukell AJ. Mexiletine: A review of its therapeutic use in painful diabetic neuropathy.

Mexiletine is an orally active local anaesthetic agent which is structurally related to lidocaine (lignocaine) and has been used for alleviating neuropathic pain of various origins. Mexiletine has been evaluated in several randomised, placebo-controlled trials in patients with painful diabetic neuropathy. The drug decreased mean visual analogue scale (VAS) pain ratings in all studies that used this measure, although in only 2 studies was this effect significantly greater than the often substantial responses seen with placebo. The clinical significance of these decreases is not clear. Statistically significant (vs placebo) reductions in VAS pain ratings were observed in 16 patients receiving mexiletine 10 mg/kg/day for 10 weeks in 1 study and in nocturnal (but not diurnal) pain in 31 patients receiving mexiletine 675 mg/day for 3 weeks in another. Retrospective analysis of another study revealed that mexiletine recipients (225 to 675 mg/day) who described their pain as stabbing, burning or formication on the pain-rating-index-total instrument of the McGill Pain Questionnaire, experienced statistically significant reductions in VAS pain scores after 5 weeks, compared with placebo recipients. Mexiletine generally did not have a significant influence on the quality of sleep in patients with diabetic neuropathy. In Japanese patients, statistically significant reductions in subjective pain ratings were achieved with mexiletine 300 mg/day in 1 study and with 450 mg/day in a further study. In controlled trials, the frequency of adverse events in patients receiving mexiletine for painful diabetic neuropathy ranged from 13.5 to 50%. Gastrointestinal complaints, of which nausea was the most frequent, were the most common adverse events in mexiletine recipients. Central nervous system complaints were uncommon, but included: sleep disturbance, headache, shakiness, dizziness and tiredness. Serious cardiac arrhythmias have not been reported in patients receiving mexiletine for painful diabetic neuropathy; however, transient tachycardia and palpitations have been reported. There are significant differences in the metabolism of mexiletine between people who have cytochrome P450 2D6 [CYP2D6; extensive metabolisers (EMs)] and those who lack this isoenzyme [poor metabolisers (PMs)]. EMs, but not PMs, are susceptible to drug interactions between mexiletine and drugs that inhibit CYP2D6 (e.g. Quinidine). Moreover, mexiletine inhibits CYP2D6-mediated metabolism of metoprolol and cytochrome P450 1A2-mediated metabolism of theophylline. Phenytoin and rifampicin (rifampin) induce the metabolism of mexiletine. Clearance of mexiletine is impaired in patients with hepatic, but not renal, dysfunction. Hence, dosage adjustments may be necessary in patients with liver disease.

Conclusions: Tricyclic antidepressants (TCAs) are the agents of choice for painful diabetic neuropathy; however, they are ineffective in approximately 50% of patients and are generally not well tolerated. Mexiletine is an alternative agent for the treatment of painful diabetic neuropathy in patients who have not had a satisfactory response to, or cannot tolerate, TCAs and/or other drugs.

Comment: Personal experience with mexiletine has generally been disappointing for painful neuropathies and neuropathic-like pain. Side effects have not been a significant problem. "Statistically significant reduction in VAS" and clinically significant pain relief are not always the same thing.

Drugs 1998;56:691-707.

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